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DOI: https://doi.org/10.1097/DAD.0b013e318289b1db

Cutaneous Lymphomas: An Update. Part 1: T-Cell and Natural Killer/T-Cell Lymphomas and Related Conditions

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Abstract: Primary cutaneous T-cell lymphomas (CTCL) represent the majority of cutaneous lymphomas (CLs) and are a spectrum of diseases with a wide variety of clinical, histological, and phenotypic features and diverse biologic behavior. This review focuses on the observations on new variants of CTCL and recent developments in deciphering the pathogenetic mechanisms, which have implication for the nosologic concepts and future classification of CLs. Variants of mycosis fungoides (MF) such as the unilesional and the papular form have been characterized in more detail. Studies analyzed the expression of CD30 and PD-1 in MF and other forms of CTCL. New variants in the group of cutaneous $CD30^+$ lymphoproliferative disorders include the epidermotropic $CD8^+$ variant of lymphomatoid papulosis (type D) and angiocentric lymphomatoid papulosis (type E), which histologically mimic aggressive lymphomas, and therefore may be diagnostically challenging. Cutaneous proliferations of T cell–expressing markers of follicular helper T cells (PD-1, CXCL-13, and bcl-6) display a prognostically heterogeneous group. There is an increasing spectrum of CTCL with the expression of CD8 by tumor cells, including $CD8^+$ MF, $CD8^+$ forms of cutaneous $CD30^+$ lymphoproliferative disorders, and $CD8^+$ small/medium-sized lymphoproliferations, which are not included as distinct entities in the World Health Organization–European Organization for Research and Treatment of Cancer for CLs and the World Health Organization classification. Unusual presentations and incomplete phenotypes of blastic neoplasm of plasmacytoid dendritic cells are discussed. Clinicopathologic correlation is mandatory for the diagnosis of primary CLs. Analysis of genetic and epigenetic alterations in CLs revealed new diagnostic markers and putative targets for therapy of aggressive forms of CLs.

Key Words: cutaneous lymphoma, lymphoproliferation, genetics, diagnosis, WHO, classification, CD8, small/medium sized, lymphomatoid papulosis

(*Am J Dermatopathol* 2014;36:105–123)

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All authors and staff in a position to control the content of this CME activity and their spouses/life partners (if any) have disclosed that they have no financial relationships with, or financial interests in, any commercial organizations pertaining to this educational activity.

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LEARNING OBJECTIVES

After completing this CME activity, physicians should be better able to:

1. Describe the morphologic and phenotypic spectrum of cutaneous T-cell lymphomas.
2. Identify new variants of cutaneous T-cell lymphomas, especially in mycosis fungoides and cutaneous CD30-positive lymphoproliferative disorders.
3. Distinguish indolent forms of cutaneous T-cell lymphomas from aggressive forms.

INTRODUCTION

Primary cutaneous lymphomas (CLs) are the second most common form of extranodal non-Hodgkin lymphomas (NHL) and represent a heterogeneous group of neoplasms with a wide spectrum of clinical, histological, and immunophenotypical features[1,2] (Table 1). The histological examination plays a crucial role and is often the starting point in the diagnostic work-up of CL. It encompasses immunophenotyping and in some CL also molecular genetic analyses. Almost all the diagnostic tests can nowadays be performed on formalin-fixed and paraffin-embedded tissues and thus became widely used. Terminology of CL should follow the current World Health Organization (WHO) classification (fourth edition, 2008), which is accepted by both hematopathologists and dermatopathologists.[3] The WHO classification integrated the unique biologic features of CL as they were described in the WHO–European Organization for Research and Treatment of Cancer (EORTC) classification for primary CL into a classification of tumors of hematopoietic and lymphoid tissues.[3] Both the WHO-EORTC classification (2005) and the current WHO classification (2008) follow the concept of defining lymphomas by their clinical, histological, immunophenotypic, and genetic features and the site of primary presentation in a multiparameter approach as it had been originally introduced by the Revised European American Lymphoma classification.[4,5] As a consequence, the clinical manifestation is emphasized as an essential element in the diagnostic approach for primary CL. The diagnosis in primary CL can therefore only be achieved by an integration of clinical, histological, immunophenotypic, and genetic findings in the context of a clinicopathologic correlation.

CUTANEOUS T-CELL LYMPHOMAS

Mycosis fungoides (MF) is the most common form of primary CL accounting for approximately 40% of all CL.

TABLE 1. WHO Classification for Lymphoid Neoplasms (Fourth Edition, 2008)*

Mature T-cell and NK-cell neoplasms
Mycosis fungoides
MF variants and subtypes
Folliculotropic MF
Pagetoid reticulosis
Granulomatous Slack Skin
Sézary Syndrome
Adult T-cell leukemia/lymphoma
Primary cutaneous $CD30^+$ T-cell lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma†
Extranodal NK/T-cell lymphoma, nasal type
Primary cutaneous peripheral T-cell, rare subtypes
Primary cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma (provisional)
Primary cutaneous γ/δ T-cell lymphoma
Primary cutaneous $CD4^+$ small/medium T-cell lymphoma (provisional)
Primary cutaneous peripheral T-cell, unspecified

*List restricted to CLs in the WHO classification.
†Phenotype (by definition): TCR alpha/beta chain positive.

According to the WHO-EORTC and the WHO classifications, MF is defined by its classic form, that is, by patches and plaques, or variants showing a similar course.[1–3]

Diagnosis of *early MF* remains one of the challenging aspects of the disease because histological findings are subtle with less prominent or even lacking atypia of lymphocytes, interface changes with vacuolization, lining-up of lymphocytes along the junctional zone.[6] A T-cell clone is only found in half of the biopsies in early disease stages. Thus, neither molecular tests for T-cell clonality nor phenotypic marker are of significant diagnostic value in early MF. Thus, clinical features are very important for the diagnosis. Using high-throughput genomic transcription profiling, Zhang et al[7] identified 19 genes with specific enrichment in early MF lesions that showed no significant upregulation in chronic dermatitis. Among the 19 genes, TOX and PDCD1 discriminated between early MF lesions and biopsies from inflammatory skin disorders by RNA expression. TOX demonstrated highly specific staining of MF cells in early MF biopsies in immunohistochemistry.[7] These data need to be confirmed in larger studies.

MF exhibits a broad and increasing spectrum of clinical, histological, and immunophenotypic variants.[8] Among those, unilesional, folliculotropic, and granulomatous variants exhibit a different course and prognosis. In contrast to classic MF in patch and plaque stages with a 5-year survival rate of more than 90%, follicular or folliculotropic MF and granulomatous MF carry an impaired prognosis with 5-year survival rates of approximately 60% and 41% by 15 years[9–12].

Clinically, folliculotropic MF usually presents with patches and plaques and hair loss within the lesions. Occasionally, the disease may manifest with predominantly papular lesions (Fig. 1). Recently, an unusual clinical

FIGURE 1. Folliculotropic MF: clinical manifestation with erythematous papular lesions on the trunk.

presentation with alopecia areata-like patchy lesions has been described, which may be diagnostically misleading and seen in up to a third of patients with MF-associated hair loss.[13,14] One has to be aware that epidermotropism into the interfollicular epidermis, which is a useful diagnostic finding for classic MF, is absent in 40%–60% of folliculotropic MF.[15] In approximately 70% of biopsies, folliculotropic MF is accompanied by follicular mucinosis (Fig. 2), but the latter may be completely absent in the remaining cases[15] (Fig. 3). Distinction of folliculotropic MF-associated follicular mucinosis from benign (idiopathic) follicular mucinosis remains challenging. Although folliculotropic MF more probably displays a dense lymphocytic infiltrate with slight nuclear atypia, an increased CD4/CD8 ratio and a clonal rearrangement of T-cell receptor (TCR) genes, the histological or phenotypic features do not allow separating the 2 entities with certainty.[16] In 2011, Magro et al[17] described a series of patients with facial

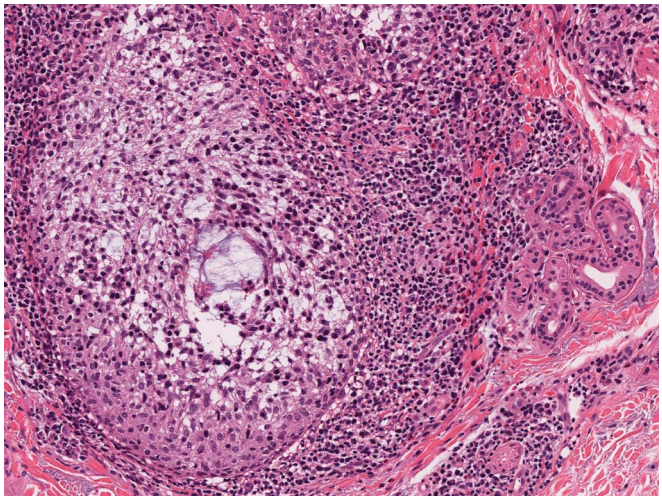

FIGURE 2. Folliculotropic MF with infiltration of hair follicles by small- to medium-sized lymphocytes and follicular mucinosis (magnification, ×100).

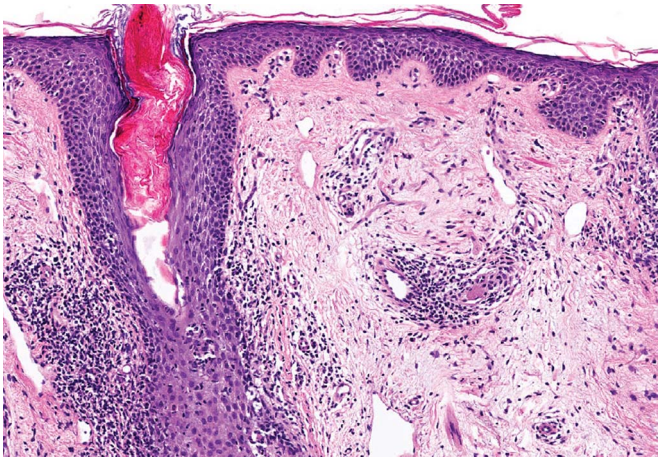

FIGURE 3. Folliculotropic MF without follicular mucinosis. Note the subtle epidermotropism (magnification, ×100).

erythematous papules resembling rosacea and/or nodules and large scaly plaques that histolopathologically manifested folliculotropic infiltrates of small lymphocytes with cerebriform nuclei, a CD4/CD8 ratio >5:1, reduced CD7 expression and monoclonal T cells in 25% of the cases. The authors proposed the term folliculotropic T-cell lymphocytosis for this condition which in their opinion represents another manifestation of T-cell dyscrasia.[18] Further studies are needed to clarify whether these cases represent folliculotropic MF or a reactive inflammatory process based on its indolent course with a median duration of 3 years. Most recently, follicular mucinosis and MF-like drug eruption has been described.[19] Folliculotropic MF must also be distinguished from rare cases of adult T-cell leukemia/lymphoma accompanied by follicular mucinosis.[20]

Similar to folliculotropic MF, prognosis of *granulomatous MF* with a 5-year survival of 66% is worse than in classic MF and granulomatous slack skin (GSS).[12] Histologically, a sarcoid-like or, more rarely, a granuloma annulare–like pattern is found.[21] The neoplastic lymphocytes are small- to medium-sized lymphocytes.[12,21] Remarkably, epidermotropism is very subtle or absent in half of the biopsies that makes the diagnosis challenging. Detection of T-cell clonality may be a useful adjunctive diagnostic marker to separate granulomatous MF from sarcoidosis.[22,23] Rare coexistence of patch stage MF and interstitial granuloma annulare in the same patient, however, may represent a diagnostic pitfall.[24,25] A granulomatous process can also be seen in follicullotropic MF with lesions presenting with destruction of follicular units and secondary granulomatous reaction.[26]

Due to overlapping histological features between granulomatous MF and GSS, distinction relies on the clinical presentation with development of bulky hanging skin folds in GSS.[12,21] Both in granulomatous MF and in GSS, there is a significantly increased risk of the development of a second lymphoid neoplasm, particularly Hodgkin lymphoma, occurring in 20%–50% of the patients.

In contrast to folliculotropic MF and granulomatous MF, *unilesional MF* represents the other end of the prognostic spectrum of MF with an excellent prognosis. Currently, however, unilesional MF is not recognized as a specific subtype in the WHO classification. A recent analysis of the literature identified approximately 130 cases of unilesional MF.[27] The mean age at diagnosis is 47 years, but patients of any age group including children can be affected. Unilesional MF presents as a solitary patch, plaque, or nodule mostly arising on the trunk or head and neck. Histologically, unilesional MF displays the typical epidermotropic lymphocytic infiltrates as seen in patch and plaque stages of classic MF. In a subset of cases, folliculotropic and syringotropic infiltrates are found.[28] Most cases display a $CD4^+$ phenotype and clonal T cells. Unilesional MF has an excellent prognosis. Development of additional noncontiguous MF lesions during course may occur but is the exception seen in only very few patients.[29] Recurrences after treatment (surgical excision and/or radiotherapy) occur in 9% of the patients. Development of tumor stage or transformation with large cells accounting for more than 25% of the infiltrate has been reported including 2 patients with folliculotropic unilesional MF, but in general, this evolution to tumor stage seems to be rare in unilesional MF.[30,31]

Pagetoid reticulosis (PR), listed as MF subtype in both WHO-EORTC and WHO classifications, shows a more prominent epidermotropism and nuclear pleomorphism compared with unilesional MF and more commonly displays a $CD8^+$ phenotype.[32] Furthermore, PR manifests more often as hyperkeratotic lesions. Nevertheless, it can be debated whether the historical term pagetoid reticulosis should be subsummarized within unilesional MF in future classifications.

Papular MF is a peculiar clinical variant of MF manifesting with papules, but not with patches or plaques.[33,34] However, the latter may arise later in the course of the disease. Like in other MF forms, histology of papular MF shows epidermotropic infiltrates of small atypical lymphocytes, which may justify considering this clinically very unusual form within the spectrum of MF. Distinction from lymphomatoid papulosis (LYP) type B, which histologically also shows epidermotropic infiltrates of small $CD4^+$ and often $CD30^-$ lymphocytes, depends on clinical features. In papular MF, the lesions persist, whereas a waxing and waning with spontaneous regression of the lesions after a few weeks is observed in LYP.

MF is a neoplasm of lymphoid cells with a $CD4^+$ T-helper (TH) phenotype and a shift from TH1 cytokines in early stages of the disease to a TH2 cytokine pattern in late stage.[35] Various phenotypes of otherwise typical MF has been described including $CD8^+$ MF, which often presents with hyper- or hypopigmented patches and plaques or $CD56^+$ MF.[8,36] Rarely, a CD4/CD8 double-negative phenotype has been observed that more frequently seems to be associated with an unusual clinical presentation such as annular MF.[37,38] Remarkably, CD4/CD8 double-negative MF expresses PD-1, a marker of follicular helper T cells in certain cases.[38] This feature may be of therapeutic relevance in the future because PD-1 may serve as a therapeutic target.

Most phenotypic MF variants seem to have no prognostic impact.[39] Recently, Edinger et al,[40] however, demonstrated that the expression of CD30 by intradermal lymphocytes and a high proliferation rate in patch and plaque stage MF are

linked to an impaired prognosis. In contrast, the expression of CD30 in tumor stage is an independent marker for a better disease-related survival.[41] Based on these data expression of CD30 should be examined in all stages of MF.

Progression of MF into tumor stage characterized by large and often ulcerated nodules occurs in only a subset of patients (10%–20%).[9] It should be distinguished from transformation histologically defined by the occurrence of large pleomorphic cells accounting for more than 25% of the lymphocytes.[42] Large cell transformation in MF is usually associated with an aggressive clinical course and poor survival, requiring aggressive therapeutic approach. To identify prognostic factors, Benner et al have recently analyzed the prognostic relevance of clinical, histological, and immunophenotypical features in a large cohort of transformed MF patients. Multivariate analysis of 75 patients with only skin lesions at the time of large cell transformation was performed and CD30 negativity, folliculotropic MF and extent of skin lesions were found to be independent parameters for both disease-specific survival and overall survival.[41] Increased Twist expression has been found in advanced stages of MF, suggesting that increased Twist expression may correlate with tumor progression.[43]

Tumor stage MF carries a characteristic molecular signature reflecting the high proliferative activity of the T cells, including altered expression of cell cycle and kinetochore regulators.[44] In addition, the molecular signature in MF tumor stage suggests that MF originates from interleukin 32–producing cells.[44] Furthermore, previously unreported therapeutic targets and/or diagnostic markers such as GTSF1 and TRIP13 were identified. Array comparative genomic hybridization revealed gains in myc gene and losses in CDKN2A, CDKN2B, and MTAP genes. Patients with tumors harboring more than 5 DNA aberrations (so-called unstable group) had a shorter overall survival.[45] The prognostic relevance of inactivation of the CDKN2A–CDKN2B was confirmed by Laharanne et al[46] who found a shorter survival in patients with transformed MF with deletion of this locus.

Sézary Syndrome

Sézary syndrome (SS) is a rare form of cutaneous T-cell lymphomas (CTCL) accounting for 3% of all CL. In contrast to MF, SS carries an unfavorable prognosis with a median survival of less than 3 years.[47–49] Several lines of evidence from molecular genetic studies support the concept that SS is different from MF and not only a leukemic form of MF.[50] It turned out that SS and MF arise from distinct T-cell subsets. T cells in SS express the lymph node homing molecules CCR7 and L-selectin and the differentiation marker CD27, a phenotype consistent with central memory T cells. T cells isolated from MF skin lesions lack CCR7/L-selectin and CD27 but strongly expressed CCR4 and CLA, a phenotype suggestive of skin resident effector memory T cells.[51] Genome-wide analysis of MF and SS also revealed different chromosomal gain and losses in the two diseases.[52] Although the histological features in SS in general are very similar to those seen in MF patch and plaque stages, the infiltrate in SS appears more monotonous. Unspecific features with only very subtle epidermotropism of atypical lymphocytes are found in up to 40% of the biopsies,

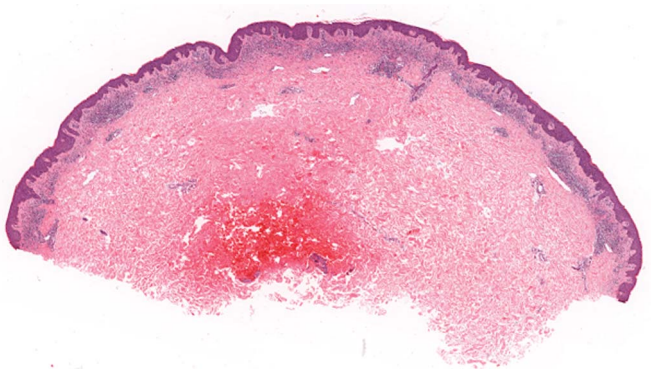

FIGURE 4. SS: band-like dense lymphocytic infiltrate in the upper demis (magnification, ×20).

which makes the histological assessment of SS challenging[53] (Figs. 4 and 5). In some cases, folliculotropic infiltrates have been observed. In some cases of SS, the biopsy tends to show more spongiotic features sometimes with eosinophils rarely seen in MF and less of the more common MF typical findings like prominent reticular fibroplasia and Pautrier collections. In addition to the most common $CD4^+$ phenotype, a majority of T cells in SS express PD-1.[54] Because this marker is also expressed by MF in variable degree, it does not serve as

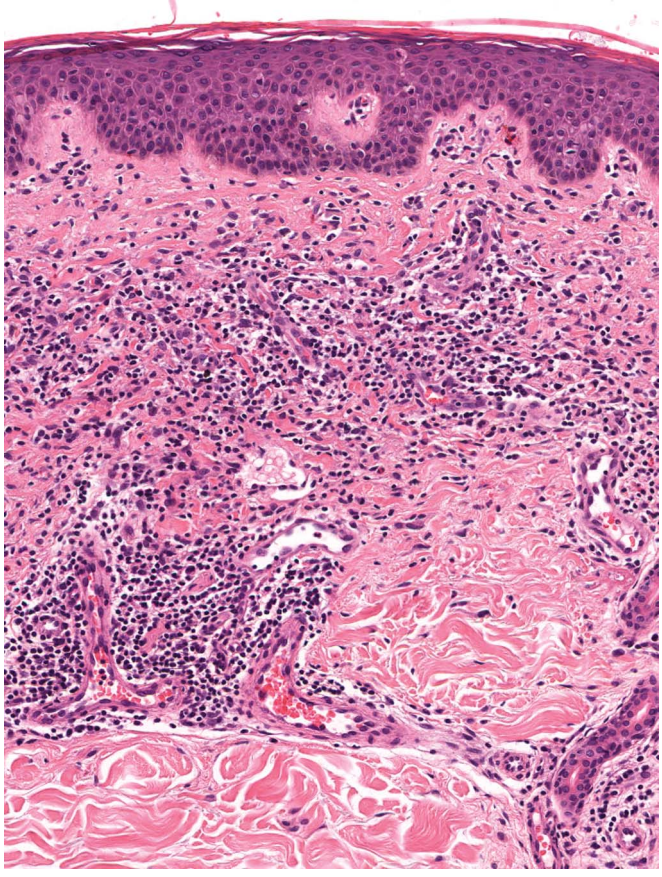

FIGURE 5. SS: perivascular and interstitial infiltrate of small lymphocytes and exocytosis of only very few lymphocytes (magnification, ×200).

a helpful diagnostic marker. The clinical features and the presence of more than 1000 cerebriform cells per milliliter peripheral blood are essential for the diagnosis of SS. There are sporadic reports on nonerythrodermic manifestation of SS including papular forms.[55]

Despite the achievements from molecular studies, the distinction of SS from erythrodermic inflammatory disorders remains a differential diagnostic problem.[56] With the exception of atypical lymphocytes, the moderate to high density of dermal infiltrates and Pautrier microabscesses, which are almost only found in SS, no morphologic parameter was found to be specific of erythrodermic forms of CTCL encompassing SS and erythrodermic MF. Single lymphocytes exocytosis, telangiectasias, and a more subtle lymphocytic dermal infiltrate were significantly more frequent in erythrodermic inflammatory conditions. A low (<10%) CD8:CD3 ratio in the epidermal lymphocytic infiltrate and dermal $CD30^+$ lymphocytes were significantly more frequent in CTCL.[56] In summary, a correct differential diagnosis between SS and an erythrodermic inflammatory dermatosis was achieved with certainty only in 57% of cases. The distinction of late-onset atopic dermatitis, red man syndrome, and pre-SS from initial SS is difficult due to overlapping clinical and histological features, hindered by the unspecific histology in up to 40% of SS biopsies, lack of widely accepted diagnostic criteria for red man syndrome, and pre-SS. Repeated biopsies are useful to increase the diagnostic accuracy.[57,58] Progression of adult-onset atopic dermatitis-like condition to overt SS in patients under immunosuppressive therapy may support the concept of pre-SS as a long-lasting premalignant condition, which may develop to full-blown SS in a state of immunosuppression.[59]

Micro-RNAs are small noncoding RNAs controlling gene expression. Five micro-RNA identified by microarray-based analysis distinguish CTCL from inflammatory skin disorders with an accuracy of more than 90%.[60] Micro-RNA represents targets for future therapeutic approaches. Among them, miR-21 is upregulated and involved in apoptosis resistance. Stimulation of Sézary cells or healthy $CD4^+$ T cells with interleukin-21 results in a strong activation of signal transducer and activator of transcription 3, which is constitutively activated in SS, and subsequent upregulation of miR-21 expression.[61]

Primary Cutaneous $CD30^+$ Lymphoproliferative Disorders

Primary cutaneous $CD30^+$ lymphoproliferative disorders ($CD30^+$ LPDs) are the second most common form (20%–25%) of cutaneous T-cell lymphoma (CTCL).[1,62] Primary cutaneous $CD30^+$ LPDs represent a spectrum of diseases including LYP, primary cutaneous anaplastic large cell lymphoma (ALCL), and so-called borderline cases.

LYP is a chronic, recurrent, and self-healing papulonecrotic or papulonodular skin eruption. Traditionally, 3 histological types are distinguished: LYP type A with scattered or grouped $CD30^+$ large pleomorphic or anaplastic lymphoid cells in the background of neutrophils and eosinophils, an epidermotropic infiltrate of small lymphocytes (type B) (Fig. 6) or cohesive sheets of atypical lymphoid cells with only a few admixed reactive cells (type C). Individual lesions may show overlapping features.[63] Furthermore, different lesions in the same patient may display different histological types. Recently, 2 new types (types D and E) have been described. Type D shows epidermotropic infiltrates of $CD8^+$ and $CD30^+$ atypical cells and mimics primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T-cell lymphoma.[64,65] We have described an angioinvasive form of LYP that manifests with rapidly evolving eschar-like ulcers (Fig. 7)—usually few at a given time—and angioinvasive infiltrates of $CD30^+$ and often $CD8^+$ medium-sized atypical lymphocytes (Fig. 8).[66] For this type, we propose the designation LYP type E. It represents a diagnostic pitfall by simulating aggressive lymphomas such as extranodal natural killer (NK)/T-cell lymphoma. Nevertheless, the lesions in LYP type E undergo spontaneous regression within a few weeks like in other LYP types. Thus, aggressive

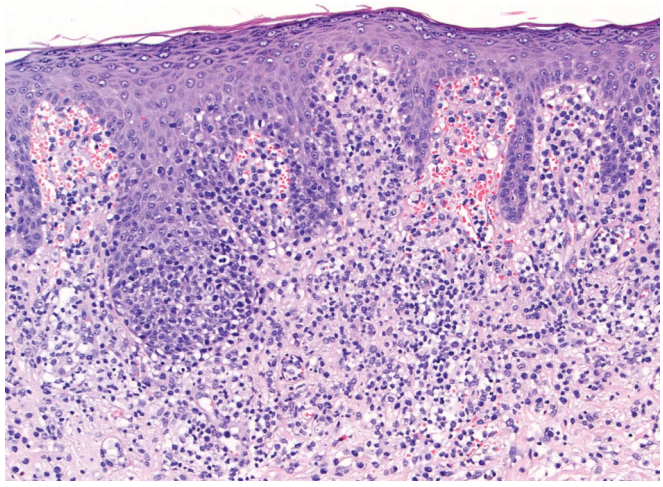

FIGURE 6. LYP (type B): epidermotropism of small-sized and a few medium-sized atypical lymphocytes. Absence of large anaplastic cells (magnification, ×200).

FIGURE 7. LYP (type E): eschar-like ulcer in the angioinvasive variant.

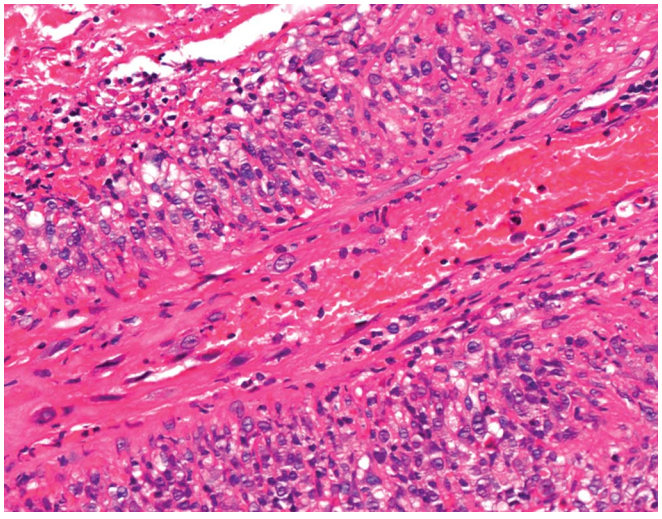

FIGURE 8. LYP (type E): angiocentric infiltrates with medium-sized to large-sized lymphocytic cells within the vessel wall. Magnification X200.

treatment should be avoided according to the recommendations for the management of CD30$^+$ LPD.[67]

Rare histopathological variants of LYP include syringotropic, granulomatous, and follicular (reviewed in Kempf[68]). Perieccrine infiltrates sometimes with effacement of the eccrine units are seen in syringotropic LYP. Noncaseating granulomas are a feature of granulomatous LYP. In so-called follicular LYP, any combination of the following features can be seen: perifollicular distribution of the infiltrate, intrafollicular CD30$^+$ cells, cystic dilatation of a hair follicle, rupture of hair follicles, hyperplasia of the follicular epithelium, follicular mucinosis, and neutrophils collection in the follicular epithelium. The latter feature accounts for pustular lesions observed clinically in these patients.[69]

There is a steadily increasing number of inflammatory and infectious disorders and neoplasms that contain a significant number of CD30$^+$ and sometimes atypical lymphocytes and thus mimic LYP clinically and/or histologically.[68,70,71] CD30$^+$ pityriasis lichenoides et varioliformis (PLEVA) histologically simulates LYP and other lymphomas.[72] Careful clinicopathologic correlation allows separating CD30$^+$ PLEVA from LYP. Nevertheless, the overlap in histological and phenotypic and genotypic features suggests that these 2 disorders may be more closely related than traditional concepts hold.[72,73] Benign atypical intravascular CD30$^+$ T-cell proliferation due to trauma or inflammation represents a reactive condition mimicking intravascular lymphoma.[74,75] This should be distinguished from the rare intravascular form of CD30$^+$ ALCL.[76]

LYP persists usually for years or even decades but is not associated with mortality. Nevertheless, patients suffering from LYP should be monitored lifelong because about 25% of the patients develop a second lymphoma, in particular Hodgkin lymphoma, MF, and primary or nodal ALCL. In addition to the expression of fascin by CD30$^+$ cells in LYP, monoclonal TCR gene rearrangement or diagnosis of LYP with histological mixed type may be prognostic indicators of disease more prone to develop those LYP-associated lymphomas.[77,78]

Primary cutaneous CD30$^+$ ALCL most commonly presents clinically with solitary nodules or tumors and on histology exhibits nodular cohesive infiltrates of large pleomorphic, anaplastic, or immunoblastic tumor cells.[1,62] By definition, more than 75% of the tumor cells express CD30.[1] Rare morphologic variants include angioinvasive, neutrophil-rich, histiocyte-rich, and sarcomatoid forms.[79–81] Neutrophil-rich CD30$^+$ has been referred to as pyogenic lymphoma.[79] A predilection of young patients has been found, with 10% of the patients experiencing extracutaneous disease progression and 18% of the patients dead at 10 months.[82] The association of pyogenic ALCL with immunesuppression and poor outcome should be validated in further studies. Few cases of intravascular CD30$^+$ ALCL have recently been reported, including primary skin disease and systemic lymphoma with secondary skin involvement.[83,84] Most recently, a myxoid variant of ALCL has been described.[85]

The most common phenotype in primary cutaneous ALCL is that of a CD4$^+$ T-helper phenotype. In rare cases, tumor cells express CD8$^+$ that seems not to be associated with an impaired prognosis.[86] By definition, more than 75% of the tumor cells express CD30. In contrast to nodal ALCL, which expresses ALK in approximately 60% of the cases, primary cutaneous ALCL are usually negative for this marker and lack the translocation $t(2;5)$.[62] Unusual cases of ALK+ primary cutaneous ALCL, however, have been reported that are associated with a translocation variant and cytoplasmic staining for ALK.[87] These rare cases may run a more aggressive course and should most probably be treated similar to systemic ALCL and could be suitable for treatment with the ALK inhibitor Crizotinib.[88]

No phenotypic marker has been confirmed to allow distinction between LYP and ALCL. In a study on the expression of chemokines receptors, expression of CXCR3 was found in a majority of LYP cases but in none of the 4 ALCL cases.[89] These data still need to be confirmed.

CD30$^+$ LPD may involve or be restricted to mucosal sites, particularly the oral cavity, orbit/conjunctiva, or nasal cavity/sinuses.[90,91] Similar cases have previously been reported as traumatic ulcerative granuloma with stromal eosinophilia.[92] Sciallis et al[91] referred to this condition as mucosal CD30$^+$ T-cell lymphoproliferations of the head and neck and demonstrated that some of the lesions show a clinicopathologic spectrum similar to cutaneous CD30$^+$ T-cell LPDs. Histological features resembled primary cutaneous ALCL accompanied in the majority of the cases by a variable number of eosinophils. Patients with mucosal or mucocutaneous disease only have a favorable prognosis and none developed systemic spread. Two cases in that series revealed rearrangements of the DUSP22-IRF4 locus on chromosome 6p25.3, detected most frequently in primary cutaneous ALCL.[93]

Genetic analysis of primary cutaneous ALCL showed gains on chromosomes 7q and 17q and losses on 6q and 13q. Peripheral T-cell lymphoma, not otherwise specified (PTL), NOS similarly showed gains on 7q and 17q but was distinguished by gains on chromosome 8 and loss of a focal overlapping region on 9p21.[94] Moreover, the study demonstrated higher expression of the skin-homing chemokine receptor genes CCR10 and CCR8 was found, which may

contribute the lower tendency to disseminate to extracutaneous sites compared with more aggressive PTL, unspecified.

Subcutaneous Panniculitis-Like T-Cell Lymphoma

This lymphoma accounts for 1% of all CL and for 75% of all subcutaneous forms of T-cell lymphomas. In the WHO-EORTC classification and the WHO classification (fourth edition, 2008), this term is by definition restricted to cases expressing a TCR alpha/beta phenotype.[1,3] Therefore, demonstration of expression of beta F1 (TCR alpha/beta) by immunohistochemistry is a pivotal diagnostic marker for this entity. Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) displays an infiltration pattern reminiscent of lobular panniculitis but is composed of small- to medium-sized lymphoid cells having slightly to moderate nuclear pleomorphism. The rimming of adipocytes by tumor cells is not disease specific and has also been shown to occur in lupus panniculitis, which is one of the major differential diagnoses. Karyorrhexis and cytophagocytosis may be present.

Immunohistochemically, SPTCL expresses $CD3^+$ $CD4^-$ $CD8^+$ $CD56^-$, TIA-1+, granzyme B+, and beta F1+.[95] SPTCL is associated with a good prognosis with 5-year survival rate of 80%.[95] Tumor spread to other tissues is rare. This is in striking contrast to cells in subcutaneous lymphoma with a γ/δ-positive TCR phenotype, which may involve the subcutaneous tissue, and should therefore be considered in the differential diagnosis (see below). The γ/δ-positive form has an unfavorable prognosis.[95,96] Clues to γ/δ-positive T-cell lymphoma include angiocentric growth, involvement of the dermis and even an epidermotropic component of the infiltrate, tumor cells with hyperchromatic nuclei, and the expression of CD56 and in particular TCR gamma. Extranodal T/NK-cell lymphoma, which may present with subcutaneous involvement, has to be considered as differential diagnosis. Demonstration of Epstein–Barr virus (EBV) by in situ hybridization is useful in discriminating this disease from SPTCL.

Due to overlapping features, relationship between lupus profundus panniculitis and SPTCL has been a subject of recent studies. Distinction between the 2 entities may be difficult, leading to the suggestion that they may belong to a spectrum of disease.[97,98] Most useful histopathological criteria for distinguishing lupus panniculitis from SPTCL included epidermal changes, lymphoid follicles with reactive germinal centers, clusters of B cells, and mixed cell infiltrate with prominent plasma cells.[99] A considerable admixture of plasma cells was found in SPTCL with concurrent or prior diagnosis of lupus erythematosus, which was not observed in the other cases of SPTCL.[95] Borreliosis manifesting as lobular panniculitis, represents a diagnostic pitfall, because the high number of $CD8^+$ lymphocytes mimics SPTCL. Moreover the plasma cells and mucin deposition and clusters of $CD123^+$ plasmacytoid dendritic cells simulate lupus panniculitis.[100]

Cutaneous Peripheral T-Cell Lymphoma, Rare Subtypes

Both in the WHO-EORTC classification and in the WHO classification, 3 lymphoma entities have been listed as provisional rare subtypes of PTL based on their characteristic clinicopathological, immunophenotypic, and prognostic features and have been separated out from PTL, unspecified: (1) primary cutaneous $CD4^+$ small/medium T-cell lymphoma ($CD4^+$ SMTL), (2) primary cutaneous $CD8^+$ aggressive epidermotropic T-cell lymphoma ($CD8^+$ AECTCL), and (3) primary cutaneous gamma/delta T-cell lymphoma (CGD-TCL).[1–3,101]

Primary Cutaneous $CD4^+$ Small/medium T-Cell Lymphoma

$CD4^+$ SMTL is listed as a provisional entity within the group of PTL in both the WHO classification (2008, fourth edition) and the WHO-EORTC classification. The relationship of $CD4^+$ SMTL to nodular T-cell pseudolymphoma and its terminology are a matter of debate and has been previously reviewed.[102] Although $CD4^+$ SMTL was originally considered a rare form of CTCL, it turned out that this lymphoproliferation is in fact much more common.[103] The most frequent clinical manifestation, which is observed in 75% of the patients, is an nonulcerated nodule arising on the head and neck area, especially on the face, and measuring up to 3 cm in diameter.[103] In a subset of patients, multiple nodules arise at different body regions. In contrast to MF, the nodules develop without preceding patches and plaques. Histologically, there are dense nodular infiltrates predominantly composed of small- and medium-sized lymphocytes, which display chromatin-dense nuclei with slight to moderate nuclear pleomorphism and a small cytoplasmic rim (Figs. 9 and 10).[103] Epidermotropism may be focally present, but it is not a prominent feature. Folliculotropism can occasionally be seen. There is an admixture of eosinophils, small clusters of plasma cells, and a variable number of macrophages occasionally forming small nonnecrotizing granulomas. Immunohistochemistry reveals expression of CD3 and CD4 by nearly all small- and medium-sized lymphocytes. There is a remarkably high number of $CD20^+$ B cells, which are found in all cases, and may be present in aggregations. In a subset of cases, a few scattered $CD30^+$ pleomorphic large lymphocytes (24%) are present. The proliferation rate ranges from 5% to 30%.[54,103] A monoclonal rearrangement of the TCR gamma gene is found in at least 60% of the cases.[103] Recent studies have indicated that $CD4^+$ SMTL

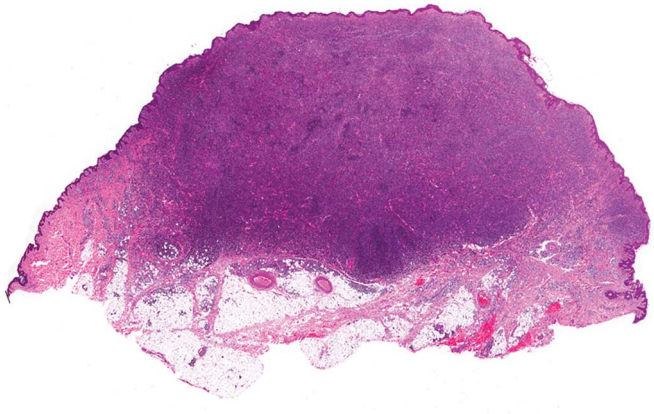

FIGURE 9. Primary cutaneous $CD4^+$ SMTL: Proliferation with dense nodular lymphocytic infiltrate. Magnification X20.

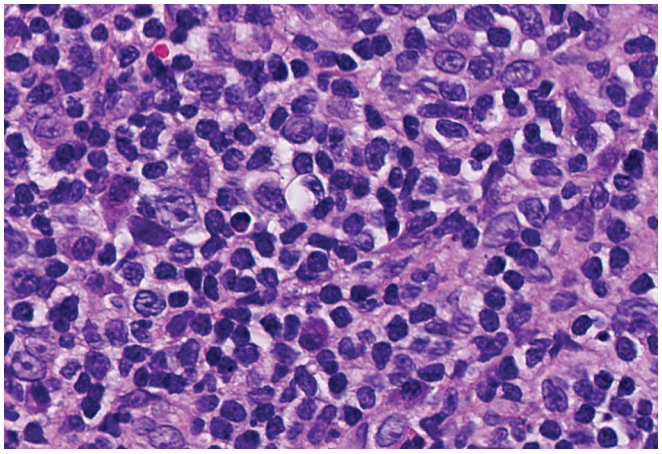

FIGURE 10. Primary cutaneous CD4+ SMTL/proliferation with small- to medium-sized lymphocytes with chromatin-dense nuclei and nuclear pleomorphism. Magnification X400.

represents a neoplastic proliferation of follicular T-helper (T_{FH}) cells based on the expression of CXCL-13 and PD-1.[104]

Due to a significant overlap of clinical and histological features, nodular T-cell pseudolymphoma and so-called pseudolymphomatous folliculitis are the most challenging differential diagnoses.[54,105] Neither the composition of the infiltrate nor the cytomorphology of the lymphocytes allow differentiating between CD4+ SMTL and nodular T-cell pseudolymphoma. Detection of clonal T cells has been reported in both disorders and therefore does not serve as a reliable discriminating diagnostic marker. In addition, PD-1 expression has recently been described in all cases of CD4+ SMTL and in nodular T-PSL.[54] Based on the overlap in clinical, histological, and phenotypic markers, some experts support the concept that most cases classified as CD4+ SMTL are identical to nodular T-PSL, at least when presenting as a solitary lesion.[54] As a consequence, the term "cutaneous nodular proliferation of pleomorphic T-lymphocytes of undetermined significance"[103] or "primary cutaneous CD4+ small/medium-sized T-cell proliferation" (R. Willemze, MD, PhD personal communication, October 2011) were proposed.

The prognosis of CD4+ SMTL in its solitary or localized form reported so far in the literature is excellent with 5-year survival rates exceeding 90%.[103,106,107] A subset of patients with CD4+ SMTL present with rapidly evolving large tumors or nodules, a higher proliferation rate of tumor cells, and a lower number of infiltrating CD8+ cells. These patients carry an impaired prognosis.[107] In patients with solitary or localized lesions, surgical excision and/or radiotherapy is the first-line therapy, whereas patients with multifocal lesions should be treated more intensively by chemotherapy.

Remarkably, nodular lymphoproliferations composed of CD8+ small- to medium-sized T cells have been reported,[108–111] which are composed of dense nodular infiltrates of small and occasionally medium-sized lymphoid cells (Figs. 11 and 12). These lymphoproliferations occur not only on the ear and on the face but also in extrafacial sites, especially on the legs. The CD8+ SMTL not only has a similar architecture and composition as the CD4+ SMTL but also

FIGURE 11. Primary cutaneous CD8+ small/medium-sized lymphoproliferative disorder: dense dermal lymphocytic infiltrates of small- to medium-sized lymphocytes (magnification, ×20).

share biologic features of CD4+ SMTL with a favorable prognosis when manifestating with a solitary lesion.[108–111] These data suggest that there is a phenotypically (CD4+ or CD8+) heterogeneous group of small- to medium-sized LPDs, which share clinical, histological, and prognostic features. For this group, we propose the term *primary cutaneous small- to medium-sized LPDs* (*CD4+ or CD8+*).[102,111]

Recently, Battistella et al[112] described *primary cutaneous follicular helper T-cell lymphoma* as a new subtype of CTCL based on the expression of follicular helper T-cell (T_{FH}) markers (CD10, Bcl-6, PD-1, CXCL-13, and ICOS) by tumor cells. In 4 of 5 patients, the disease manifested with multiple papules, plaques, and nodules predominantly on the trunk and the head. In contrast to CD4+ SMTL, primary cutaneous follicular helper T-cell lymphoma usually presents with multiple lesions and the infiltrates are mostly composed of medium- to large-sized atypical T cells. The disease was resistant to multiagent chemotherapy in patients with multifocal lesions. Gammon and Guitart[113] have reported 3 patients with rapidly evolving intertriginous tumoral lesions of nonepidermotropic infiltrates of medium-sized T cells with expression of follicular helper T cells. The authors referred to the findings as intertriginous MFs. In regard to the absence of preceding patches and the finding of nonepidermotropic infiltrates, we consider this CTCL to be related to the recently described follicular helper T-cell lymphomas. Further studies are needed to clarify the relationship of this newly proposed CTCL to CD4+ SMTL with which it shares some histological and phenotypic features.

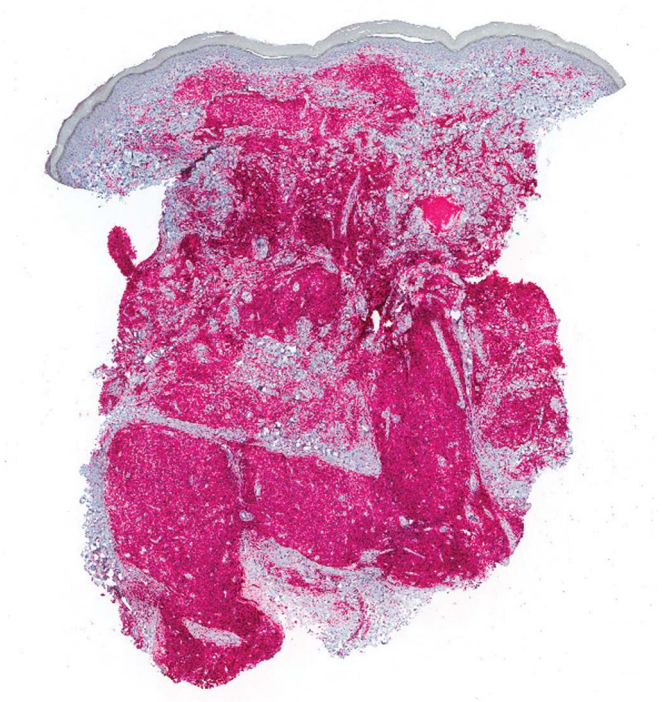

FIGURE 12. Primary cutaneous CD8+ small/medium-sized LPD: expression of CD8 by the vast majority of the infiltrate (magnification, ×20).

Primary Cutaneous CD8+ Aggressive Epidermotropic Cytotoxic T-Cell Lymphoma

Since the first description by Berti,[114] less than 50 cases of this rare and aggressive form of CD8+ CTCL have been reported in the literature. The current diagnostic criteria for CD8+ AECTCL include short history, widespread lesions, epidermotropism of pleomorphic T cells, a CD8+/CD4− phenotype, and an aggressive course as essential diagnostic elements.[115] This rare lymphoma shows predilection for men (male:female ratio approximately 2:1), with most patients being affected in their fifth to seventh decade (age ranges at diagnosis from 19 to 83 years). In typical cases, the disease manifests with widespread erosive patches, plaques, or papules and nodules undergoing necrosis and ulceration[114] (Fig. 13). Less common are hyperkeratotic patches and plaques and annular lesions, but, recently, the occurrence of pustules during disease course have also been described.[116] CD8+ AECTCL shows a short history with rapidly progressing skin lesions and spread to extracutaneous sites, particularly oral mucosa, visceral organs (lung), and central nervous system. The lymph nodes are usually not involved. The disease runs an aggressive course with a median survival of less than 32 months and a 5-year survival rate of 18%.[114,115] Only a small subset of patients seems to have a less aggressive course.[117] Multiagent chemotherapy is not very effective and followed by rapid relapse. Combination of chemotherapy and autologous stem cell transplantation may be a promising strategy to control the disease.[115]

A histological hallmark is prominent epidermotropism of small–medium or medium–large lymphocytes with pleomorphic chromatin-dense nuclei (Fig. 14). Numerous apoptotic keratinocytes and spongiosis are common features. Blister formation is occasionally seen. Extension of the lymphocytic infiltrates into the deeper dermis and subcutis, angiocentric growth, and destruction of adnexal structures may be seen but are rare.

The tumor cells express CD3+, CD4− CD8+, CD45RA+, CD45RO−, TIA-1+, and beta F1+.[114,115,118] CD30 is typically negative (E. Berti, MD, PhD personal communication, January 2013). There is no association with EBV.

CD8+ AECTCL has a broad differential diagnosis. CD8+ MF is also characterized by a band-like and epidermotropic infiltrate but displays only very few or no necrotic keratinocytes and no epidermal necrosis. CD8+ MF is characterized clinically by hyper- or hypopigmented patches and plaques and often affects young patients. In contrast to CD8+ AECTCL, no erosions, necroses, or ulcerations are seen. CD8+ MF has the same favorable prognosis as classic MF.[119] Pagetoid reticulosis, which may express CD8 and CD30,

FIGURE 13. Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma: patches and plaques with erosions and hemorrhagic crusts (by courtesy of Prof D. Metze, Germany).

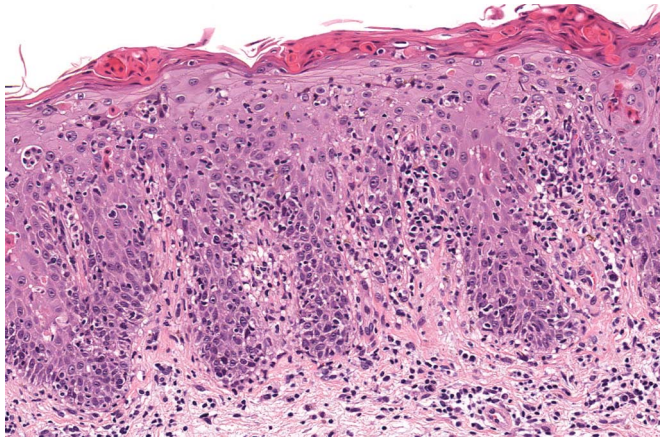

FIGURE 14. Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma: epidermotropism of medium-sized lymphocytes with moderately chromatin-dense pleomorphic nuclei (magnification, ×200).

histologically closely imitates CD8+ AECTCL, but it is by definition characterized by a solitary lesion and runs an indolent course. Clinical manifestation with self-regressing and recurrent papules and small nodules distinguishes the recently described LYP type D from CD8+ AECTCL.[64] Additionally, lymphocytes in LYP type D express CD30 in 90% of the cases and lack the expression of CD45RA.[64,65] PLEVA with the expression of CD8 represents a further challenging histological differential diagnosis due to numerous necrotic keratinocytes and epidermotropism.[72] Lack of significant nuclear atypia, and the clinical presentation with scaly macules allow distinction of PLEVA from CD8+ AECTCL.

Primary Cutaneous gamma/delta T-Cell Lymphoma

CGD-TCL is a rare malignancy characterized by a clonal proliferation of mature activated γ/δ T cells.[101] The γ/δ T cells represent a small subset (<5%) of all lymphocytes found in the peripheral blood. These cells are essential part of the innate immunity and play an important role in immunosurveillance. They express the γ/δ TCR and cytotoxic molecules. Additionally, when activated, γ/δ T cells can express 1 or more NK-associated surface molecules (CD56, CD16, and CD57), and in the activated stage, the cells become large and granular.[120] The γ/δ T cells are only exceptionally encountered in cutaneous inflammatory and neoplastic lymphocytic infiltrates.[121] Neoplastic proliferations of γ/δ T cells comprise hepatosplenic and primary cutaneous forms.[122,123]

Approximately 100 cases of primary cutaneous γ/δ+ T-cell lymphoma have been reported to date. There are neither age nor gender predilection. Generalized often necrotic or ulcerated papules, plaques, or nodules are seen clinically.[122,124] Involvement of oral mucosa is common and other extranodal sites may become involved, but lymph nodes, spleen, and bone marrow are usually spared. The patients often have B symptoms. The disease may be accompanied by a hemophagocytic syndrome, especially in patients with the subcutaneous form of the disease.[95,122,125] Hemophagocytosis syndrome is defined by fever, splenomegaly, cytopenia, hypertriglyceridemia, and/or hypofibrinogenemia, elevated serum ferritin and CD25+ cells and evidence of hemophagocytic histiocytosis in bone marrow, spleen, or lymph nodes.[126] It is accompanied by production of large amounts of interferon gamma.[95,127]

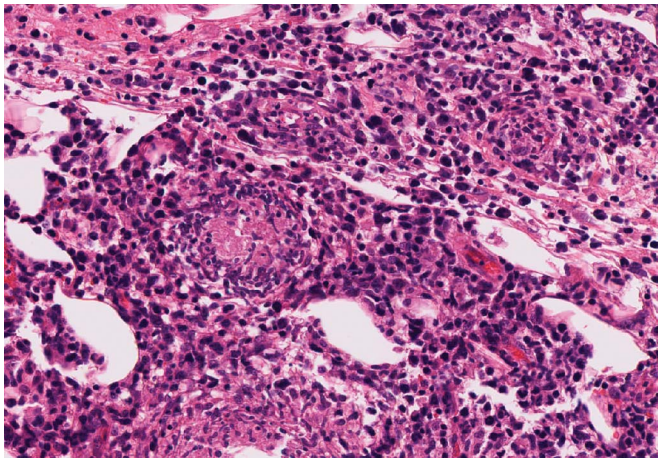

FIGURE 15. Subcutaneous gamma/delta lymphoma. Subcutaneous infiltrate of lymphocytes with atypical chromatin-dense nuclei (magnification, ×200).

Histologically, the disease manifests with the following patterns: epidermotropic (pagetoid), dermal (diffuse or nodular), and/or subcutaneous. An overlap is sometimes seen, especially in the subcutaneous form, in which the predominantly subcutaneous infiltrates are often accompanied by a dermal and an epidermotropic component.[95,124] In the subcutaneous forms, a predominantly lobular infiltrate composed of medium- to large-sized with irregular chromatin-dense or vesicular nuclei is observed (Fig. 15). Angioinvasion and necrosis are common features.[128] Immunophenotypically, the tumor cells exhibit a CD2+, CD3+, CD56+ phenotype and are often CD4/CD8 double negative. Cytotoxic molecules (TIA-1, granzyme B, perforin) are typically expressed. In addition, the expression of CD7 may be found. As the defining criterion, the neoplastic cells in primary CGD-TCL express TCR γ/δ (TCRd +) and lack TCR α/β (betaF1). The γ/δ+ TCR phenotype can be demonstrated by expression of TCR gamma on fresh-frozen tissue or formalin-fixed, paraffin-embedded sections or indirectly by the lack of beta F1 expression. Molecular studies reveal clonal rearrangement of TCR gamma or delta genes. Isochromosome 7q is a common genetic abnormality. EBV is generally negative, but isolated EBV+ cases of primary CGD-TCL have been documented.[129]

Epidermotropic forms of primary CGD-TCL may simulate MF and its subtype pagetoid reticulosis but expression of TCRγ+ allows the correct diagnosis. This is also the case for the subcutaneous form of γ/δ+ T-cell lymphoma that should be distinguished from SPTCL. The latter expresses a TCR α/β+ phenotype that is the main discriminating feature. Lymphocytic infiltrates in SPTCL are almost exclusively restricted to the subcutis that is a helpful clue on histological examination. The differential diagnosis of subcutaneous gamma/delta T-cell lymphoma also includes extranodal NK/T-cell lymphoma, nasal type. The latter is associated with EBV and displays a CD3ε+, CD56+ phenotype. However, recently, an unusual case of a CD56+ CTCL exhibiting immunophenotypic characteristics of both γ/δ T-cell lymphoma and extranodal NK/T-cell lymphoma, nasal type, has been reported.[130] The clinical course of primary CGD-TCL is aggressive with a median survival of 15 months and a 5-year survival rate of 33%.[131] The lymphoma responds poorly to multiagent chemotherapy, but hematopoietic stem cells transplantation may provide a promising strategy.[132] Remarkably, few reports identified a less aggressive form of the disease that can be controlled by ultraviolet light treatment in combination with steroids, retinoids, or methotrexate.[133,134]

Cutaneous Peripheral T-Cell Lymphoma, Unspecified/NOS

The terminology has been confusing and underwent changes with each new lymphoma classification. According to the WHO-EORTC classification and the current WHO classification, PTL, NOS represents a phenotypically and

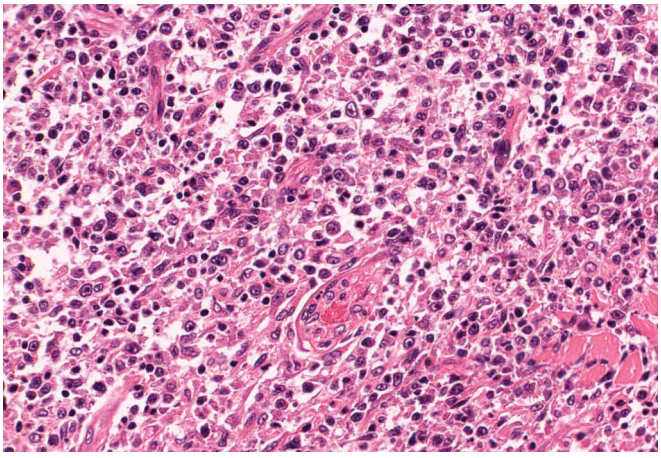

FIGURE 16. Peripheral T-cell lymphoma, not otherwise specified: cohesive infiltrates of large lymphoid cells with nuclear pleomorphism. Some of the tumor cells have an immunoblast-like cytomorphology (magnification, ×400).

prognostically heterogeneous group of CTCL that do not fit into any of the well-defined CTCL subtypes. To date, only very few case series and case reports have been documented in the literature. PTL, NOS manifests with solitary, grouped, or disseminated nodules without preceding patches or plaques.[106] PTL, NOS presenting with solitary large ulceration has been described.[135] Histologically, tumors are characterized by diffuse or nodular dense infiltrates composed of variably sized, mostly medium- to large-sized lymphoid cells with pleomorphic nuclei and pale cytoplasm. Tumor cells may display an immunoblast-like morphology (Fig. 16).[106] Angiocentric infiltrates can be observed. Epidermotropism has been reported as a feature in a few cases.[136] Eosinophils and plasma cells are admixed.[137] Tumor cells exhibit a T-cell phenotype CD2, CD3, and CD5 accompanied by loss of T-cell antigens such as CD7. Tumor cells in PTL, NOS may be CD4 or $CD8^+$ or $CD8^-$. Cytotoxic phenotypes have been reported.[135,136,138] By definition, the majority of tumor cells does not express CD30.[1] Molecular biologic assays reveal a clonal rearrangement of TCR genes.

The differential diagnosis of PTL, NOS primarily includes transformation of MF. Clinical presentation with patches and plaques preceding transformation distinguishes MF from PTL, NOS. Secondary cutaneous involvement by nodal PTL has to be excluded by staging examinations. Primary or secondary cutaneous ALCL is defined by the expression of CD30 by at least 75% of tumor cells, whereas in PTL, NOS, the expression of CD30 is absent or restricted to less than 30% of the tumor cells. The phenotype of neoplastic cells allows differentiating PTL, NOS from extranodal NK/T-cell lymphoma ($CD3\varepsilon^+$, $CD56^+$, and association with EBV) and γ/δ T-cell lymphoma (TCRγ+). Especially in patients of Asian origin or from the Caribbean region, HTLV-1– or HTLV-2–associated adult T-cell lymphoma/leukemia has to be distinguished by serology and/or molecular studies demonstrating integration of the virus into the host genome of tumor cells.

The prognosis of PTL, NOS is poor with a 5-year survival rate of less than 20%.[1,106,139] Complete remission after chemotherapy and radiotherapy are usually of short duration and followed by relapses.[106] Patients with solitary or localized skin lesions rapidly develop widespread disease. Recent molecular studies revealed differences in chromosomal alterations, the expression of chemokine receptors, and apoptosis regulators between PTL, NOS and primary cutaneous ALCL that may account for the aggressive course of PTL, NOS.[94]

Extranodal NK/T-Cell Lymphoma, Nasal-Type, and Related Conditions

Extranodal NK/T-cell lymphoma, nasal type, is a rare aggressive form of primary CL that shares immunophenotypical characteristics with normal NK cells and characteristically displays a strong expression of CD56 and cytotoxic proteins such as perforin, granzyme B, or TIA-1.[140,141] The TCR/CD3 complex is not expressed on the surface. Clonal episomal presence of EBV is typically found. TCR genes are usually in germline configuration. Histology shows dense diffuse infiltrates (Fig. 17). Angiocentric and angiodestructive growth resulting in necroses and ulceration is often found. The tumor cells are of variable size ranging from small to large cells with pleomorphic nuclei and pale cytoplasms. Mitoses are common. Occasionally, numerous admixed reactive cells such as eosinophils, plasma cells, and histiocytes are observed. Extranodal NK/T-cell lymphoma may be associated with pseudoepitheliomatous hyperplasia.

Hydroa vacciniformia–like lymphoma is a rare variant of EBV+ NK/T-cell lymphoma mostly seen in the Central and South America. The disease shows predilection for young adults and children and commonly involves sun-exposed areas where rapid progression from edema to blisters and ulcers and, finally, scarring is observed.[142,143] Facial swelling is a typical feature. Extracutaneous symptoms such as fever, hepatosplenomegaly, lymphadenopathy, and an increased high lactate dehydrogenase (LDH) level can occur. Often, the disease follows a protracted course, eventually leading to an aggressive phase characterized by concurrent infections and disease

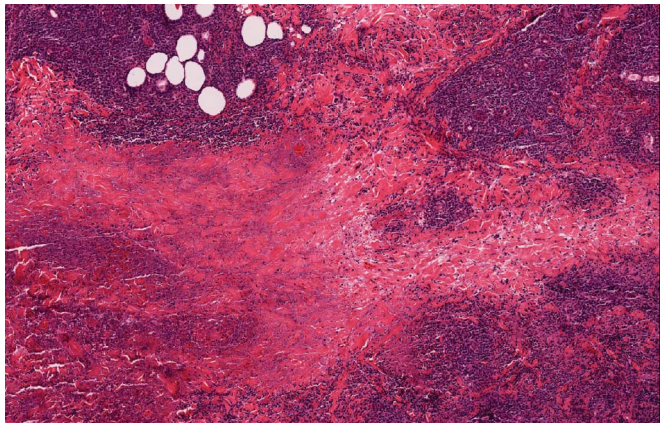

FIGURE 17. Extranodal NK/T-cell lymphoma: infiltrates of small- to medium-sized lymphocytes with chromatin-dense nuclei. Note central necrosis (magnification, ×100).

progression. In a recent series from Peru, 10 of 14 patients died after a mean follow-up of 11.6 months.[144] There have been few reports in the recent literature on cutaneous EBV+ NK/T-cell lymphoid proliferations that were different—either phenotypically or by showing an unusual clinical course—from both classic extranodal NK/T-cell lymphoma, nasal type, and hydroa vacciniformia–like lymphoma, suggesting that the spectrum of these conditions might be broader.[145,146]

Blastic Plasmacytoid Dendritic Cell Neoplasm

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) had traditionally been included in CL classifications under designations blastic NK-cell lymphoma and agranular $CD4^+$ $CD56^+$ hematodermic neoplasm. This neoplasm, however, is derived from plasmacytoid dendritic cells,[147,148] hence its name BPDCN. The disease usually presents with rapidly evolving disseminated contusiform or bruise-like patches and plaques. Manifestation with a solitary skin lesion is rare. Involvement of the oral mucosa is common. Leukemic involvement may be or may be not present at the time of the occurrence of skin lesions but occurs in 70% of the patients during disease course.[147]

Histologically, there is a diffuse or multinodular monotonous infiltrate, which sometimes is bandlike in the upper and mid dermis with column-like extensions into the deeper dermis and subcutis. The tumor cells resemble blasts with fine-dispersed chromatin. Spilling between collagen bundles is sometimes seen at the periphery of the infiltrate. Extensive intratumoral erythrocyte extravasation is usually found between the tumor cells, which account for the characteristic clinical contusiform aspect. In initial lesions, a perivascular infiltrate can be observed that may be mistaken as an inflammatory skin disorder such as erythema annulare centrifugum or drug eruption (Figs. 18 and 19).

Immunophenotypically, the neoplastic cells displays a unique phenotype with the expression of CD4, CD56, CD123, and TCL-1.[147] TdT is variably expressed. Recently, new antibodies recognizing PDC-related antigens and working on paraffin sections became available, namely BDCA-2, BCL11a, and CD2AP.

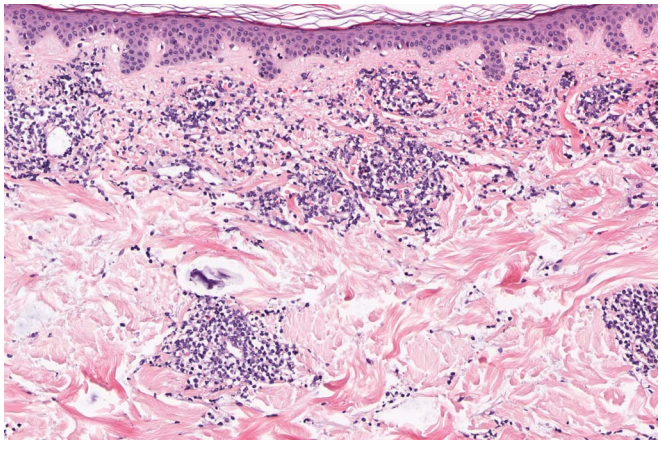

FIGURE 18. Blastic plasmacytoid dendritic cell neoplasm: unusual histological presentation with perivascular infiltrates in the upper and mid dermis. Note the extravasated erythrocytes (magnification, ×100).

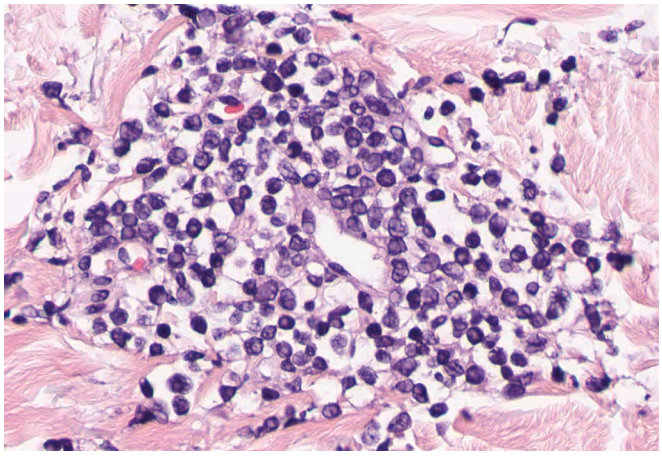

FIGURE 19. Blastic plasmacytoid dendritic cell neoplasm: perivascular infiltrates of tumor cells with finely dispersed chromatin, (magnification, ×400).

The data on genetics of this neoplasm are scarce. Recently, genetic alterations involving chromosomes 5, 6, 9, 12, 13, and 15 have been identified using array comparative genomic hybridization confirmed by fluorescence in situ hybridization analysis, but no specific genetic marker has been found.[149] The above study has also confirmed the capability of the neoplastic cells to secrete interferon-1, demonstrated by biologic interferon-1 activity of cultured cells and immunohistochemical expression of Mx-1 protein.[149] In a series of 21 cases studied by array comparative genomic hybridization, complete or partial chromosomal losses largely outnumbered the gains, with common deleted regions involving 9p21.3 (CDKN2A/CDKN2B), 13q13.1-q14.3 (RB1), 12p13.2-p13.1 (CDKN1B), 13q11-q12 (LATS2), and 7p12.2 (IKZF1) regions. Biallelic loss of locus 9p21.3 was statistically significant for a lower survival.[150]

This dendritic cell neoplasm is associated with a poor prognosis.[147,148] In some patients, the disease develops in the context of myelodysplastic syndrome or has been associated with chronic monomyelocytic leukemia.[151] The distinction of BPDCN from the latter may be challenging for 2 reasons. First, a dermal infiltrate of plasmacytoid dendritic cells may occasionally occur in a patient suffering from a myeloid neoplasm, a phenomenon poorly understood at present.[152] Second, chronic monomyelocytic leukemia seems to be a heterogeneous disorder with a subtype similar if not identical to BPDCN.[153] The concomitant occurrence of cutaneous BPDCN and cutaneous B-cell LPD has been reported indicating that BPDCN may be associated with lymphoid neoplasms.[154] This article provides an overview of the spectrum of cutaneous T- and NK/T-cell lymphomas including recently identified new morphologic and phenotypic variants of these lymphomas and discusses diagnostic and prognostic markers in indolent and aggressive forms of cutaneous T-cell lymphomas.

REFERENCES

1. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005;105:3768–3785.

2. Burg G, Jaffe ES, Kempf W, et al. WHO/EORTC classification of cutaneous lymphomas. In: LeBoit P, Burg G, Weedon D, et al, eds. *World Health Organization Classification of Tumours. Pathology and Genetics of Skin Tumors*. Lyon, France: WHO IARC, 2006:166.
3. Swerdlow SH, Campo E, Harris NL, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: IARC Press, 2008.
4. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood*. 1994;84:1361–1392.
5. Harris NL, Jaffe ES, Vardiman JW, et al. WHO classification of tumours of hematopoietic and lympoid tissues: introduction. In: Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: IARC Press, 2008:12–13.
6. Massone C, Kodama K, Kerl H, et al. Histopathologic features of early (patch) lesions of mycosis fungoides: a morphologic study on 745 biopsy specimens from 427 patients. *Am J Surg Pathol.* 2005;29: 550–560.
7. Zhang Y, Wang Y, Yu R, et al. Molecular markers of early-stage mycosis fungoides. *J Invest Dermatol.* 2012;132:1698–1706.
8. Kazakov DV, Burg G, Kempf W. Clinicopathological spectrum of mycosis fungoides. *J Eur Acad Dermatol Venereol.* 2004;18:397–415.
9. van Doorn R, Van Haselen CW, van Voorst Vader PC, et al. Mycosis fungoides: disease evolution and prognosis of 309 Dutch patients. *Arch Dermatol.* 2000;136:504–510.
10. Flaig MJ, Cerroni L, Schuhmann K, et al. Follicular mycosis fungoides. A histopathologic analysis of nine cases. *J Cutan Pathol.* 2001;28:525–530.
11. van Doorn R, Scheffer E, Willemze R. Follicular mycosis fungoides, a distinct disease entity with or without associated follicular mucinosis: a clinicopathologic and follow-up study of 51 patients. *Arch Dermatol.* 2002;138:191–198.
12. Kempf W, Ostheeren-Michaelis S, Paulli M, et al. Granulomatous mycosis fungoides and granulomatous slack skin: a multicenter study of the Cutaneous Lymphoma Histopathology Task Force Group of the European Organization For Research and Treatment of Cancer (EORTC). *Arch Dermatol.* 2008;144:1609–1617.
13. Iorizzo M, El Shabrawi Caelen L, Vincenzi C, et al. Folliculotropic mycosis fungoides masquerading as alopecia areata. *J Am Acad Dermatol.* 2010;63:e50–e52.
14. Bi MY, Curry JL, Christiano AM, et al. The spectrum of hair loss in patients with mycosis fungoides and Sezary syndrome. *J Am Acad Dermatol.* 2011;64:53–63.
15. Lehman JS, Cook-Norris RH, Weed BR, et al. Folliculotropic mycosis fungoides: single-center study and systematic review. *Arch Dermatol.* 2010;146:607–613.
16. Rongioletti F, De Lucchi S, Meyes D, et al. Follicular mucinosis: a clinicopathologic, histochemical, immunohistochemical and molecular study comparing the primary benign form and the mycosis fungoides-associated follicular mucinosis. *J Cutan Pathol.* 2010;37:15–19.
17. Magro CM, Crowson AN. Folliculotropic T-cell lymphocytosis as a distinct form of pilotropic T-cell dyscrasia. *Am J Clin Pathol.* 2011;135:221–229.
18. Guitart J, Magro C. Cutaneous T-cell lymphoid dyscrasia: a unifying term for idiopathic chronic dermatoses with persistent T-cell clones. *Arch Dermatol.* 2007;143:921–932.
19. Shalin SC, Brantley J, Hafeez Diwan J. Follicular mucinosis and mycosis-fungoides-like drug eruption due to leuprolide acetate: a case report and review. *J Cutan Pathol.* 2012;39:1022–1025.
20. Camp B, Horwitz S, Pulitzer MP. Adult T-cell leukemia/lymphoma with follicular mucinosis: an unusual histopathological finding and a commentary. *J Cutan Pathol.* 2012;39:861–865.
21. Scarabello A, Leinweber B, Ardigo M, et al. Cutaneous lymphomas with prominent granulomatous reaction: a potential pitfall in the histopathologic diagnosis of cutaneous T- and B-cell lymphomas. *Am J Surg Pathol.* 2002;26:1259–1268.
22. Dabiri S, Morales A, Ma L, et al. The frequency of dual TCR-PCR clonality in granulomatous disorders. *J Cutan Pathol.* 2011;38:704–709.
23. Pfaltz K, Kerl K, Palmedo G, et al. Clonality in sarcoidosis, granuloma annulare, and granulomatous mycosis fungoides. *Am J Dermatopathol.* 2011;33:659–662.
24. Cota C, Ferrara G, Cerroni L. Granuloma annulare with prominent lymphoid infiltrates ("pseudolymphomatous" granuloma annulare). *Am J Dermatopathol.* 2012;34:259–262.
25. Koochek A, Fink-Puches R, Cerroni L. Coexistence of patch stage mycosis fungoides and interstitial granuloma annulare in the same patient: a pitfall in the clinicopathologic diagnosis of mycosis fungoides. *Am J Dermatopathol.* 2012;34:198–202.
26. Gerami P, Rosen S, Kuzel T, et al. Folliculotropic mycosis fungoides: an aggressive variant of cutaneous T-cell lymphoma. *Arch Dermatol.* 2008;144:738–746.
27. Ally MS, Pawade J, Tanaka M, et al. Solitary mycosis fungoides: a distinct clinicopathologic entity with a good prognosis: a series of 15 cases and literature review. *J Am Acad Dermatol.* 2012;67:736–744.
28. Pileri A, Facchetti F, Rutten A, et al. Syringotropic mycosis fungoides: a rare variant of the disease with peculiar clinicopathologic features. *Am J Surg Pathol.* 2011;35:100–109.
29. Hodak E, Phenig E, Amichai B, et al. Unilesional mycosis fungoides: a study of seven cases. *Dermatology*. 2000;201:300–306.
30. Setyadi HG, Nash JW, Duvic M. The solitary lymphomatous papule, nodule, or tumor. *J Am Acad Dermatol.* 2007;57:1072–1083.
31. Kempf W, Kazakov DV, Schermesser M, et al. Unilesional follicular mycosis fungoides: report of two cases with progression to tumor stage and review of the literature. *J Cutan Pathol.* 2012;39:853–860.
32. Haghighi B, Smoller BR, LeBoit PE, et al. Pagetoid reticulosis (Woringer-Kolopp disease): an immunophenotypic, molecular, and clinicopathologic study. *Mod Pathol.* 2000;13:502–510.
33. Kodama K, Fink-Puches R, Massone C, et al. Papular mycosis fungoides: a new clinical variant of early mycosis fungoides. *J Am Acad Dermatol.* 2005;52:694–698.
34. Martorell-Calatayud A, Botella-Estrada R, Sanmartin-Jimenez O, et al. Papular mycosis fungoides: two new cases of a recently described clinicopathological variant of early mycosis fungoides. *J Cutan Pathol.* 2010;37:330–335.
35. Chong BF, Wilson AJ, Gibson HM, et al. Immune function abnormalities in peripheral blood mononuclear cell cytokine expression differentiates stages of cutaneous T-cell lymphoma/mycosis fungoides. *Clin Cancer Res.* 2008;14:646–653.
36. Pavlovsky L, Mimouni D, Amitay-Laish I, et al. Hyperpigmented mycosis fungoides: an unusual variant of cutaneous T-cell lymphoma with a frequent CD8+ phenotype. *J Am Acad Dermatol.* 2012;67: 69–75.
37. Hodak E, David M, Maron L, et al. CD4/CD8 double-negative epidermotropic cutaneous T-cell lymphoma: an immunohistochemical variant of mycosis fungoides. *J Am Acad Dermatol.* 2006;55:276–284.
38. Kempf W, Kazakov DV, Cipolat C, et al. CD4/CD8 double negative mycosis fungoides with PD-1 (CD279) expression-A disease of follicular helper T-cells? *Am J Dermatopathol.* 2012;34:757–761.
39. Massone C, Crisman G, Kerl H, et al. The prognosis of early mycosis fungoides is not influenced by phenotype and T-cell clonality. *Br J Dermatol.* 2008;159:881–886.
40. Edinger JT, Clark BZ, Pucevich BE, et al. CD30 expression and proliferative fraction in nontransformed mycosis fungoides. *Am J Surg Pathol.* 2009;33:1860–1868.
41. Benner MF, Jansen PM, Vermeer MH, et al. Prognostic factors in transformed mycosis fungoides: a retrospective analysis of 100 cases. *Blood*. 2012;119:1643–1649.
42. Salhany KE, Cousar JB, Greer JP, et al. Transformation of cutaneous T cell lymphoma to large cell lymphoma. A clinicopathologic and immunologic study. *Am J Pathol.* 1988;132:265–277.
43. Goswami M, Duvic M, Dougherty A, et al. Increased Twist expression in advanced stage of mycosis fungoides and Sezary syndrome. *J Cutan Pathol.* 2012;39:500–507.
44. van Kester MS, Borg MK, Zoutman WH, et al. A meta-analysis of gene expression data identifies a molecular signature characteristic for tumor-stage mycosis fungoides. *J Invest Dermatol.* 2012;132:2050–2059.
45. Salgado R, Servitje O, Gallardo F, et al. Oligonucleotide array-CGH identifies genomic subgroups and prognostic markers for tumor stage mycosis fungoides. *J Invest Dermatol.* 2010;130:1126–1135.
46. Laharanne E, Chevret E, Idrissi Y, et al. CDKN2A-CDKN2B deletion defines an aggressive subset of cutaneous T-cell lymphoma. *Mod Pathol.* 2010;23:547–558.

47. Willemze R, Kerl H, Sterry W, et al. EORTC classification for primary cutaneous lymphomas: a proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment of Cancer. *Blood*. 1997;90:354–371.
48. Caudron A, Marie-Cardine A, Bensussan A, et al. New developments in Sezary syndrome. *Ann Dermatol Venereol.* 2012;139:31–40.
49. Kubica AW, Davis MD, Weaver AL, et al. Sezary syndrome: a study of 176 patients at Mayo Clinic. *J Am Acad Dermatol.* 2012;67:1189–1199.
50. van Doorn R, van Kester MS, Dijkman R, et al. Oncogenomic analysis of mycosis fungoides reveals major differences with Sezary syndrome. *Blood*. 2009;113:127–136.
51. Campbell JJ, Clark RA, Watanabe R, et al. Sezary syndrome and mycosis fungoides arise from distinct T-cell subsets: a biologic rationale for their distinct clinical behaviors. *Blood*. 2010;116:767–771.
52. Laharanne E, Oumouhou N, Bonnet F, et al. Genome-wide analysis of cutaneous T-cell lymphomas identifies three clinically relevant classes. *J Invest Dermatol.* 2010;130:1707–1718.
53. Trotter MJ, Whittaker SJ, Orchard GE, et al. Cutaneous histopathology of Sezary syndrome: a study of 41 cases with a proven circulating T-cell clone. *J Cutan Pathol.* 1997;24:286–291. Issn: 0303-6987.
54. Cetinozman F, Jansen PM, Willemze R. Expression of programmed death-1 in primary cutaneous CD4-positive small/medium-sized pleomorphic T-cell lymphoma, cutaneous pseudo-T-cell lymphoma, and other types of cutaneous T-cell lymphoma. *Am J Surg Pathol.* 2012; 36:109–116.
55. Iqbal K, Bott J, Robson A, et al. Nonerythrodermic Sezary syndrome. *Clin Exp Dermatol.* 2011;36:207–208.
56. Ram-Wolff C, Martin-Garcia N, Bensussan A, et al. Histopathologic diagnosis of lymphomatous versus inflammatory erythroderma: a morphologic and phenotypic study on 47 skin biopsies. *Am J Dermatopathol.* 2010;32:755–763.
57. Zip C, Murray S, Walsh NM. The specificity of histopathology in erythroderma. *J Cutan Pathol.* 1993;20:393–398.
58. Walsh NM, Prokopetz R, Tron VA, et al. Histopathology in erythroderma: review of a series of cases by multiple observers. *J Cutan Pathol.* 1994;21: 419–423.
59. Sokolowska-Wojdylo M, Baranska-Rybak W, Cegielska A, et al. Atopic dermatitis-like pre-Sezary syndrome: role of immunosuppression. *Acta Derm Venereol.* 2011;91:574–577.
60. Ralfkiaer U, Hagedorn PH, Bangsgaard N, et al. Diagnostic microRNA profiling in cutaneous T-cell lymphoma (CTCL). *Blood*. 2011;118: 5891–5900.
61. van der Fits L, van Kester MS, Qin Y, et al. MicroRNA-21 expression in CD4+ T cells is regulated by STAT3 and is pathologically involved in Sezary syndrome. *J Invest Dermatol.* 2011;131:762–768.
62. Kempf W, Willemze R, Jaffe ES, et al. CD30+ T-cell lymphoproliferative disorders. In: LeBoit P, Burg G, Weedon D, et al, eds. *World Health Organization Classification of Tumours. Pathology and Genetics of Skin Tumours*. Lyon, France: IARC Press, 2006:179–181.
63. El Shabrawi-Caelen L, Kerl H, Cerroni L. Lymphomatoid papulosis: reappraisal of clinicopathologic presentation and classification into subtypes A, B, and C. *Arch Dermatol.* 2004;140:441–447.
64. Saggini A, Gulia A, Argenyi Z, et al. A variant of lymphomatoid papulosis simulating primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma. Description of 9 cases. *Am J Surg Pathol.* 2010;34:1168–1175.
65. Cardoso J, Duhra P, Thway Y, et al. Lymphomatoid papulosis type D: a newly described variant easily confused with cutaneous aggressive CD8-positive cytotoxic T-cell lymphoma. *Am J Dermatopathol.* 2012;34:762–765.
66. Kempf W, Kazakov DV, Schaerer L, et al. Angioinvasive lymphomatoid papulosis: a new variant simulating aggressive lymphomas. *Am J Surg Pathol.* 2013;37:1–13.
67. Kempf W, Pfaltz K, Vermeer MH, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. *Blood.* 2011;118:4024–4035.
68. Kempf W. CD30 positive lymphoproliferative disorders—histopathology, differential diagnosis, new variants and simulators. *J Cutan Pathol.* 2006;33(Suppl 1):58–70.
69. Kempf W, Kazakov DV, Baumgartner H, et al. Follicular lymphomatoid papulosis: a study of 11 cases, with new histopathological findings. *J Am Acad Dermatol.* 2013; Pii: S0190-9622(12) 02331-02336.
70. Cepeda LT, Pieretti M, Chapman SF, et al. CD30-positive atypical lymphoid cells in common non-neoplastic cutaneous infiltrates rich in neutrophils and eosinophils. *Am J Surg Pathol.* 2003;27:912–918.
71. Werner B, Massone C, Kerl H, et al. Large CD30-positive cells in benign, atypical lymphoid infiltrates of the skin. *J Cutan Pathol.* 2008;35:1100–1107.
72. Kempf W, Kazakov DV, Palmedo G, et al. Pityriasis lichenoides et varioliformis acuta with numerous CD30+ cells: a variant mimicking lymphomatoid papulosis and other cutaneous lymphomas. A clinicopathologic, immunohistochemical, and molecular biological study of 13 cases. *Am J Surg Pathol.* 2012;36:1021–1029.
73. Vonderheid EC, Kadin ME, Gocke CD. Lymphomatoid papulosis followed by pityriasis lichenoides: a common pathogenesis? *Am J Dermatopathol.* 2011;33:835–840.
74. Baum CL, Stone MS, Liu V. Atypical intravascular CD30+ T-cell proliferation following trauma in a healthy 17-year-old male: first reported case of a potential diagnostic pitfall and literature review. *J Cutan Pathol.* 2009;36:350–354.
75. Riveiro-Falkenbach E, Fernandez-Figueras MT, Rodriguez-Peralto JL. Benign atypical intravascular CD30+ T-cell proliferation: a reactive condition mimicking intravascular lymphoma. *Am J Dermatopathol.* 2013;35:143–150.
76. Zizi-Sermpetzoglou A, Petrakopoulou N, Tepelenis N, et al. Intravascular T-cell lymphoma of the vulva, CD30 positive: a case report. *Eur J Gynaecol Oncol.* 2009;30:586–588.
77. Kempf W, Levi E, Kamarashev J, et al. Fascin expression in cutaneous CD30-positive lymphoproliferative disorders. *J Cutan Pathol.* 2002;29: 295–300.
78. de Souza A, El-Azhary RA, Camilleri MJ, et al. In search of prognostic indicators for lymphomatoid papulosis: a retrospective study of 123 patients. *J Am Acad Dermatol.* 2012;66:928–937.
79. Burg G, Kempf W, Kazakov DV, et al. Pyogenic lymphoma of the skin: a peculiar variant of primary cutaneous neutrophil-rich CD30+ anaplastic large-cell lymphoma. Clinicopathological study of four cases and review of the literature. *Br J Dermatol.* 2003;148:580–586.
80. Boudova L, Kazakov DV, Jindra P, et al. Primary cutaneous histiocyte and neutrophil-rich CD30+ and CD56+ anaplastic large-cell lymphoma with prominent angioinvasion and nerve involvement in the forehead and scalp of an immunocompetent woman. *J Cutan Pathol.* 2006;33: 584–589.
81. Massone C, El-Shabrawi-Caelen L, Kerl H, et al. The morphologic spectrum of primary cutaneous anaplastic large T-cell lymphoma: a histopathologic study on 66 biopsy specimens from 47 patients with report of rare variants. *J Cutan Pathol.* 2008;35:46–53.
82. Papalas JA, Van Mater D, Wang E. Pyogenic variant of primary cutaneous anaplastic large-cell lymphoma: a lymphoproliferative disorder with a predilection for the immunocompromised and the young. *Am J Dermatopathol.* 2010;32:821–827.
83. Rieger KE, Polidore T, Warnke R, et al. ALK-negative systemic intravascular anaplastic large cell lymphoma presenting in the skin. *J Cutan Pathol.* 2011;38:216–220.
84. Wang L, Li C, Gao T. Cutaneous intravascular anaplastic large cell lymphoma. *J Cutan Pathol.* 2011;38:221–226.
85. Gable AD, Clark SH, Magro CM. Myxoid variant of anaplastic large cell lymphoma involving the skin: a case report. *J Cutan Pathol.* 2012; 39:787–790.
86. Plaza JA, Ortega P, Lynott J, et al. CD8-positive primary cutaneous anaplastic large T-cell lymphoma (PCALCL): case report and review of this unusual variant of PCALCL. *Am J Dermatopathol.* 2010;32: 489–491.
87. Kadin ME, Pinkus JL, Pinkus GS, et al. Primary cutaneous ALCL with phosphorylated/activated cytoplasmic ALK and novel phenotype: EMA/MUC1+, cutaneous lymphocyte antigen negative. *Am J Surg Pathol.* 2008;32:1421–1426.
88. Lamant L, Pileri S, Sabattini E, et al. Cutaneous presentation of ALK-positive anaplastic large cell lymphoma following insect bites: evidence for an association in five cases. *Haematologica*. 2010;95:449–455.
89. Suga H, Sugaya M, Miyagaki T, et al. Differential patterns of CXCR3, CCR3, and CCR10 expression in mycosis fungoides, Sezary syndrome and CD30(+) lymphoproliferative disorders: immunohistochemical study of 43 samples. *J Dermatol Sci.* 2011;64:142–144.

90. Agarwal M, Shenjere P, Blewitt RW, et al. CD30-positive T-cell lymphoproliferative disorder of the oral mucosa–an indolent lesion: report of 4 cases. *Int J Surg Pathol.* 2008;16:286–290.
91. Sciallis AP, Law ME, Inwards DJ, et al. Mucosal CD30-positive T-cell lymphoproliferations of the head and neck show a clinicopathologic spectrum similar to cutaneous CD30-positive T-cell lymphoproliferative disorders. *Mod Pathol.* 2012;25:983–992.
92. Hirshberg A, Amariglio N, Akrish S, et al. Traumatic ulcerative granuloma with stromal eosinophilia: a reactive lesion of the oral mucosa. *Am J Clin Pathol.* 2006;126:522–529.
93. Pham-Ledard A, Prochazkova-Carlotti M, Laharanne E, et al. IRF4 gene rearrangements define a subgroup of CD30-positive cutaneous T-cell lymphoma: a study of 54 cases. *J Invest Dermatol.* 2010;130:816–825.
94. van Kester MS, Tensen CP, Vermeer MH, et al. Cutaneous anaplastic large cell lymphoma and peripheral T-cell lymphoma NOS show distinct chromosomal alterations and differential expression of chemokine receptors and apoptosis regulators. *J Invest Dermatol.* 2010;130:563–575.
95. Willemze R, Jansen PM, Cerroni L, et al. Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. *Blood.* 2008;111:838–845.
96. Santucci M, Pimpinelli N, Massi D, et al. Cytotoxic/natural killer cell cutaneous lymphomas. *Cancer.* 2003;97:610–627.
97. Magro CM, Crowson AN, Kovatich AJ, et al. Lupus profundus, indeterminate lymphocytic lobular panniculitis and subcutaneous T-cell lymphoma: a spectrum of subcuticular T-cell lymphoid dyscrasia. *J Cutan Pathol.* 2001;28:235–247.
98. Pincus LB, LeBoit PE, McCalmont TH, et al. Subcutaneous panniculitis-like T-cell lymphoma with overlapping clinicopathologic features of lupus erythematosus: coexistence of 2 entities? *Am J Dermatopathol.* 2009;31:520–526.
99. Massone C, Kodama K, Salmhofer W, et al. Lupus erythematosus panniculitis (lupus profundus): clinical, histopathological, and molecular analysis of nine cases. *J Cutan Pathol.* 2005;32:396–404.
100. Kempf W, Kazakov DV, Kutzner H. Lobular panniculitis due to Borrelia burgdorferi infection mimicking subcutaneous panniculitis-like T-cell lymphoma. *Am J Dermatopathol.* 2013;35:e30–e33.
101. Gaulard P, Berti E, Willemze R, et al. Primary cutaneous peripheral T-cell lymphomas, rare subtypes. In: *WHO Classification of Tumors of the Haematopoietic and Lymphoid Tissues*. Lyon, France: IARC Press, 2008:302–305.
102. Kempf W, Rozati S, Kerl K, et al. Cutaneous peripheral T-cell lymphomas, unspecified/NOS and rare subtypes: a heterogeneous group of challenging cutaneous lymphomas. *G Ital Dermatol Venereol.* 2012;147:553–562.
103. Beltraminelli H, Leinweber B, Kerl H, et al. Primary cutaneous CD4+ small-/medium-sized pleomorphic T-cell lymphoma: a cutaneous nodular proliferation of pleomorphic T lymphocytes of undetermined significance? A study of 136 cases. *Am J Dermatopathol.* 2009;31:317–322.
104. Rodriguez Pinilla SM, Roncador G, Rodriguez-Peralto JL, et al. Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma expresses follicular T-cell markers. *Am J Surg Pathol.* 2009;33:81–90.
105. Kazakov DV, Belousova IE, Kacerovska D, et al: Hyperplasia of hair follicles and other adnexal structures in cutaneous lymphoproliferative disorders: a study of 53 cases, including so-called pseudolymphomatous folliculitis and overt lymphomas. *Am J Surg Pathol.* 2008;32:1468–1478.
106. Bekkenk MW, Vermeer MH, Jansen PM, et al. Peripheral T-cell lymphomas unspecified presenting in the skin: analysis of prognostic factors in a group of 82 patients. *Blood.* 2003;102:2213–2219.
107. Garcia-Herrera A, Colomo L, Camos M, et al. Primary cutaneous small/medium CD4+ T-cell lymphomas: a heterogeneous group of tumors with different clinicopathologic features and outcome. *J Clin Oncol.* 2008;26:3364–3371.
108. Petrella T, Maubec E, Cornillet-Lefebvre P, et al. Indolent CD8-positive lymphoid proliferation of the ear: a distinct primary cutaneous T-cell lymphoma? *Am J Surg Pathol.* 2007;31:1887–1892.
109. Beltraminelli H, Mullegger R, Cerroni L. Indolent CD8+ lymphoid proliferation of the ear: a phenotypic variant of the small-medium pleomorphic cutaneous T-cell lymphoma? *J Cutan Pathol.* 2010;37:81–84.
110. Suchak R, Verdolini R, Robson A, et al. Extragenital lichen sclerosus et atrophicus mimicking cutaneous T-cell lymphoma: report of a case. *J Cutan Pathol.* 2010;37:982–986.
111. Kempf W, Kazakov DV, Cozzio A, et al. Primary cutaneous CD8+ small to medium-sized lymphoproliferative disorder in extrafacial sites—clinicopathological features and concepts on their classification. *Am J Dermatopathol.* 2013;35:159–166.
112. Battistella M, Beylot-Barry M, Bachelez H, et al. Primary cutaneous follicular helper T-cell lymphoma: a new subtype of cutaneous T-cell lymphoma reported in a series of 5 cases. *Arch Dermatol.* 2012;148:832–839.
113. Gammon B, Guitart J. Intertriginous mycosis fungoides: a distinct presentation of cutaneous T-cell lymphoma that may be caused by malignant follicular helper T cells. *Arch Dermatol.* 2012;148:1040–1044.
114. Berti E, Tomasini D, Vermeer MH, et al. Primary cutaneous CD8-positive epidermotropic cytotoxic T cell lymphomas. A distinct clinicopathological entity with an aggressive clinical behavior. *Am J Pathol.* 1999;155:483–492.
115. Nofal A, Abdel-Mawla MY, Assaf M, et al. Primary cutaneous aggressive epidermotropic CD8(+) T-cell lymphoma: proposed diagnostic criteria and therapeutic evaluation. *J Am Acad Dermatol.* 2012;67:748–759.
116. Ito Y, Goto M, Hatano Y, et al. Epidermotropic CD8+ cytotoxic T-cell lymphoma exhibiting a transition from the indolent to the aggressive phase, accompanied by emergence of CD7+ cells and formation of neutrophilic pustules. *Clin Exp Dermatol.* 2012;37:128–131.
117. Massone C, Chott A, Metze D, et al. Subcutaneous, blastic natural killer (NK), NK/T-cell, and other cytotoxic lymphomas of the skin: a morphologic, immunophenotypic, and molecular study of 50 patients. *Am J Surg Pathol.* 2004;28:719–735.
118. Gormley RH, Hess SD, Anand D, et al. Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma. *J Am Acad Dermatol.* 2010;62:300–307.
119. Nikolaou VA, Papadavid E, Katsambas A, et al. Clinical characteristics and course of CD8+ cytotoxic variant of mycosis fungoides: a case series of seven patients. *Br J Dermatol.* 2009;161:826–830.
120. Havran WL, Boismenu R. Activation and function of gamma delta T cells. *Curr Opin Immunol.* 1994;6:442–446.
121. Hocker TL, Wada DA, El-Azhary R, et al. Expression of T-cell receptor-gammadelta in normal human skin, inflammatory dermatoses and mycosis fungoides. *J Cutan Pathol.* 2012;39:419–424.
122. Tripodo C, Iannitto E, Florena AM, et al. Gamma-delta T-cell lymphomas. *Nat Rev Clin Oncol.* 2009;6:707–717.
123. Guitart J, Weisenburger DD, Subtil A, et al. Cutaneous gammadelta T-cell lymphomas: a spectrum of presentations with overlap with other cytotoxic lymphomas. *Am J Surg Pathol.* 2012;36:1656–1665.
124. Berti E, Cerri A, Cavicchini S, et al. Primary cutaneous gamma/delta T-cell lymphoma presenting as disseminated pagetoid reticulosis. *J Invest Dermatol.* 1991;96:718–723.
125. Chakrapani A, Avery A, Warnke R. Primary cutaneous gamma delta T-cell lymphoma with brain involvement and hemophagocytic syndrome. *Am J Dermatopathol.* 2013;35:270–272.
126. Henter JI, Elinder G, Ost A. Diagnostic guidelines for hemophagocytic lymphohistiocytosis. The FHL Study Group of the Histiocyte Society. *Semin Oncol.* 1991;18:29–33.
127. Burg G, Dummer R, Wilhelm M, et al. A subcutaneous delta-positive T-cell lymphoma that produces interferon gamma. *N Engl J Med.* 1991;325:1078–1081.
128. Arnulf B, Copie-Bergman C, Delfau-Larue MH, et al. Nonhepatosplenic gammadelta T-cell lymphoma: a subset of cytotoxic lymphomas with mucosal or skin localization. *Blood.* 1998;91:1723–1731.
129. Caudron A, Bouaziz JD, Battistella M, et al. Two atypical cases of cutaneous gamma/delta T-cell lymphomas. *Dermatology.* 2011;222:297–303.
130. Schieke SM, Sharaf MA, Lerner A, et al. Primary cutaneous CD56 positive lymphoma: a diagnostic conundrum in an unusual case of lymphoma. *J Cutan Pathol.* 2012;39:540–544.
131. Toro JR, Liewehr DJ, Pabby N, et al. Gamma-delta T-cell phenotype is associated with significantly decreased survival in cutaneous T-cell lymphoma. *Blood.* 2003;101:3407–3412.
132. Duarte RF, Schmitz N, Servitje O, et al. Haematopoietic stem cell transplantation for patients with primary cutaneous T-cell lymphoma. *Bone Marrow Transplant.* 2008;41:597–604.

133. Nakashima H, Sugaya M, Minatani Y, et al. Cutaneous gamma/delta T-cell lymphoma treated with retinoid and narrowband ultraviolet B. *Clin Exp Dermatol.* 2009;34:e345–e346.
134. Fujii M, Uehara J, Honma M, et al. Primary cutaneous gammadelta-T-cell lymphoma treated with low-dose methotrexate and narrowband ultraviolet B irradiation: report of a case with testicular involvement. *J Dermatol.* 2010;38:368–372.
135. Reich A, Maj J, Schlue J, et al. Primary cutaneous peripheral T-cell non-Hodgkin lymphoma, not otherwise specified, with cytotoxic features. *Int J Dermatol.* 2010;49:967–969.
136. Yamamoto M, Nakada T, Iijima M. Primary cutaneous T-cell lymphoma, unspecified, exhibiting an aggressive clinical course and a cytotoxic phenotype. *Int J Dermatol.* 2008;47:720–722.
137. Joly P, Vasseur E, Esteve E, et al. Primary cutaneous medium and large cell lymphomas other than mycosis fungoides. An immunohistological and follow-up study on 54 cases. French Study Group for Cutaneous Lymphomas. *Br J Dermatol.* 1995;132:506–512.
138. Hagiwara M, Takata K, Shimoyama Y, et al. Primary cutaneous T-cell lymphoma of unspecified type with cytotoxic phenotype: clinicopathological analysis of 27 patients. *Cancer Sci.* 2009;100:33–41.
139. Beljaards RC, Meijer CJ, Van der Putte SC, et al. Primary cutaneous T-cell lymphoma: clinicopathological features and prognostic parameters of 35 cases other than mycosis fungoides and CD30-positive large cell lymphoma. *J Pathol.* 1994;172:53–60.
140. Chan JKC, Quintanilla-Martinez L, Ferry JA, et al. Extranodal NK/T-cell lymphoma, nasal type. In: Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO Classification of Tumours of Haematopietic and Lymphoid Tissues*. Lyon, France: IARC Press, 2008:285–288.
141. Berti E, Recalcati S, Girgenti V, et al. Cutaneous extranodal NK/T-cell lymphoma: a clinicopathologic study of 5 patients with array-based comparative genomic hybridization. *Blood*. 2010;116:165–170.
142. Magana M, Sangueza P, Gil Beristain J, et al. Angiocentric cutaneous T-cell lymphoma of childhood (hydroa-like lymphoma): a distinctive type of cutaneous T-cell lymphoma. *J Am Acad Dermatol.* 1998;38:574–579.
143. Barrionuevo C, Anderson VM, Zevallos-Giampietri E, et al. Hydroa-like cutaneous T-cell lymphoma: a clinicopathologic and molecular genetic study of 16 pediatric cases from Peru. *Appl Immunohistochem Mol Morphol.* 2002;10:7–14.
144. Rodriguez-Pinilla SM, Barrionuevo C, Garcia J, et al. EBV-associated cutaneous NK/T-cell lymphoma: review of a series of 14 cases from Peru in children and young adults. *Am J Surg Pathol.* 2010;34:1773–1782.
145. Park S, Lee DY, Kim WS, et al. Primary cutaneous Epstein-Barr virus-associated T-cell lymphoproliferative disorder-2 cases with unusual, prolonged clinical course. *Am J Dermatopathol.* 2010;32:832–836.
146. Zhang G, Bai HX, Yang L, et al. NK-/T-cell lymphoma resembling hydroa vacciniforme with positive CD4 marker expression: a diagnostic difficulty. *Am J Dermatopathol.* 2013;35:94–97.
147. Petrella T, Bagot M, Willemze R, et al. Blastic NK-cell lymphomas (agranular CD4+CD56+ hematodermic neoplasms): a review. *Am J Clin Pathol.* 2005;123:662–675.
148. Facchetti F, Jones DM, Petrella T. Blastic plasmacytoid dendritic cell neoplasm. In: Swerdlow SH, Campo E, Harris NL, et al, eds. *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: IARC Press, 2008:145–147.
149. Petrella T, Herve G, Bonnotte B, et al. Alpha-interferon secreting blastic plasmacytoid dendritic cells neoplasm: a case report with histological, molecular genetics and long-term tumor cells culture studies. *Am J Dermatopathol.* 2012;34:626–631.
150. Lucioni M, Novara F, Fiandrino G, et al. Twenty-one cases of blastic plasmacytoid dendritic cell neoplasm: focus on biallelic locus 9p21.3 deletion. *Blood*. 2011;118:4591–4594.
151. Kazakov DV, Mentzel T, Burg G, et al. Blastic natural killer-cell lymphoma of the skin associated with myelodysplastic syndrome or myelogenous leukaemia: a coincidence or more? *Br J Dermatol.* 2003;149:869–876.
152. Dargent JL, Delannoy A, Pieron P, et al. Cutaneous accumulation of plasmacytoid dendritic cells associated with acute myeloid leukemia: a rare condition distinct from blastic plasmacytoid dendritic cell neoplasm. *J Cutan Pathol.* 2011;38:893–898.
153. Vitte F, Fabiani B, Benet C, et al. Specific skin lesions in chronic myelomonocytic leukemia: a spectrum of myelomonocytic and dendritic cell proliferations. A study of 42 cases. *Am J Surg Pathol.* 2012;36:1302–1316.
154. Patel JL, Shetty S, Salama ME. An unusual case of cutaneous blastic plasmacytoid dendritic cell neoplasm with concomitant B-cell lymphoproliferative disorder. *Am J Dermatopathol.* 2011;33:e31–e36.

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CME EXAMINATION
FEBRUARY 2014

Please mark your answers on the ANSWER SHEET.

After completing this CME activity, physicians should be better able to describe the morphologic and phenotypic spectrum of cutaneous T-cell lymphomas, identify new variants of cutaneous T-cell lymphomas, especially in mycosis fungoides and cutaneous CD30-positive lymphoproliferative disorders, and distinguish indolent forms of cutaneous T-cell lymphomas from aggressive forms.

1. Which statement on mycosis fungoides (MF) is true?

a) MF with a CD8-positive phenotype carries a poor prognosis.
b) Unilesional MF most commonly displays a CD8-positive phenotype.
c) Folliculotropic and granulomatous MF have an impaired prognosis.
d) B-cells are consistently absent in early MF and serve as a diagnostic marker to distinguish MF from inflammatory disorders.

2. A patient presents with erythroderma, peripheral lymphadenopathy, palmar and plantar keratosis, and loss of pubic and axillary hairs. What is the most likely diagnosis?

a) Psoriatic erythroderma
b) Sezary syndrome
c) Acute T-lymphoblastic lymphoma/leukemia
d) Actinic reticuloid

3. Which statement regarding primary cutaneous CD30+ anaplastic large cell lymphoma (ALCL) is true?

a) ALCL most commonly presents with multiple nodules with predilection for the extremities.
b) By definition, 50% of the tumor cells have to express CD30.
c) Primary cutaneous ALCL usually lacks the translocation t(2;5).
d) Expression of CD8 by the tumor cells is associated with a poor prognosis.

4. Subcutaneous panniculitis-like T-cell lymphoma has, in general, a very good prognosis (5-year survival > 80%). To distinguish it from more aggressive variants of subcutaneous gamma/delta T-cell lymphoma, it is pivotal to demonstrate:

a) Clusters of CD123 positive cells
b) BetaF1 positive phenotype
c) Angiocentric growth pattern
d) EBV positivity

5. Which statement is correct?

a) Primary cutaneous CD8-positive aggressive epidermotropic T-cell lymphoma typically lacks expression of CD45RA.
b) Cutaneous gamma delta T-cell lymphoma is associated with Epstein Barr virus in the majority of cases.
c) Tumor cells in subcutaneous panniculitis like T-cell lymphoma usually express CD4 and CD56.
d) The CD4+ T-cells in primary cutaneous CD4-positive small/medium T-cell lymphoma express PD-1.

6. The neoplastic cells in blastic neoplasm of plasmacytoid dendritic cells, which is derived from plasmacytoid dendritic cells, display a specific phenotype Which combination of markers is typically expressed by the tumor cells?

a) CD8, TIA-1, CD123, TCL-1
b) CD3, CD21, CD79a, CD123
c) CD7, CD56, CD123, EBV
d) CD4, CD56, CD123, TCL-1

ANSWER SHEET FOR THE AMERICAN JOURNAL OF DERMATOPHATHOLOGY
CME PROGRAM EXAM
February 2014

Please answer the questions on page 121 by filling in the appropriate circles on the answer sheet below. Please mark the one best answer and fill in the circle until the letter is no longer visible. To process your exam, you must also provide the following information:

Name (please print): _____
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1. (A) (B) (C) (D) (E)
2. (A) (B) (C) (D) (E)
3. (A) (B) (C) (D) (E)
4. (A) (B) (C) (D) (E)
5. (A) (B) (C) (D) (E)
6. (A) (B) (C) (D) (E)

Your evaluation of this CME activity will help guide future planning. Please respond to the following questions below.

Please rate these activities (1 — minimally, 5 — completely)	1 2 3 4 5
These activities were effective in meeting the educational objectives	O O O O O
These activities were appropriately evidence-based	O O O O O
These activities were relevant to my practice	O O O O O

Please rate your ability to achieve the following objectives, both before and after this activity: 1 (minimally) to 5 (completely)	Pre 1 2 3 4 5	Post 1 2 3 4 5
1. Describe the morphologic and phenotypic spectrum of cutaneous T-cell lymphomas	O O O O O	O O O O O
2. Identify new variants of cutaneous T-cell lymphomas, especially in mycosis fungoides and cutaneous CD30-positive lymphoproliferative disorders	O O O O O	O O O O O
3. Distinguish indolent forms of cutaneous T-cell lymphomas from aggressive forms.	O O O O O	O O O O O

How many of your patients are likely to be impacted by what you learned from this activity?
O <20% O 20-40% O 40-60% O 60-80% O >80%

Do you expect that these activities will help you improve your skill or judgment within the next 6 months? (1 — definitely will not change, 5 — definitely will change)	1 2 3 4 5	1 2 3 4 5
	O O O O O	O O O O O

How will you apply what you learned from these activities (mark all that apply):

In diagnosing patients O	In making treatment decisions O
In monitoring patients O	As a foundation to learn more O
In educating students and colleagues O	In educating patients and their caregivers O
As part of a quality or performance improvement project O	To confirm current practice O
For maintenance of board certification O	For maintenance of licensure O

How committed are you to applying these activities to your practice in the ways you indicated above? (1 — minimally, 5 — completely)	1 2 3 4 5
	O O O O O

Did you perceive any bias for or against any commercial products or devices?	Yes	No
If yes, please explain:	O	O

How long did it take you to complete these activities? _____ hours _____ minutes
What are your biggest clinical challenges related to dermatopathology?

[ ] Yes! I am interested in receiving future CME programs from Lippincott CME Institute! (Please place a check mark in the box)

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